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DISTRIBUTION OF WATER AND SALTS IN THE HUMAN ORGANS DURING FEVER

ERNST PRIBRAM, M.D.
Professor of Experimental Medicine in the University of Vienna
CHICAGO

PHYSIOLOGIC REQUIREMENTS FOR DISTRIBUTION OF WATER AND SALTS IN LIVING CELLS

All living cells of the human body are very rich in water. This is not imbibed from preexistent capillaries, but is a constituent part of the cell protoplasm, absorbed by molecular imbibition (Fick[1]). The contents of a living cell consist generally in (*a*) specific protoplasm, (*b*) nonspecific substances (reserve substances and metabolic products). The specific cell protoplasm consists of colloids assimilated by the organism; it has a high surface tension and a constant amount of imbibed water during life. Any change of its composition and water contents may indicate a pathologic stage, if not the death of the cell. The water contents of all other cell colloids—reserve substances and metabolic products—vary between certain limits. The amount of specific protoplasm and other cell colloids is different in different cells, depending on their differentiation and function. Cells of low differentiation, leukocytes for instance, are rich in nonspecific colloids; cells of high differentiation, as red blood corpuscles, consist chiefly of specific cell protoplasm. All changes of water distribution which will be mentioned in this article are probably limited to the nonspecific cell contents. The scheme in figure 1 may facilitate the survey of the distribution of all cell contents and their relation to the water and the substances dissolved in water.

The distribution of the water in the cell contents is the outcome of the mutual solubility of their constituents. This solubility depends (1) on the character of the colloids. Proteins take up more water than other colloids. Fats are insoluble in water, but in combination with lipoids or with protein they participate in the water adsorption, reducing the water adsorption of the colloid, with which they combine. (2) The solubility depends further on the presence, the amount and the character

1. Fick, A.: Med. Physik, 1830.

of the crystalloids dissolved in the water. These have a different influence on different colloids. Protein, for instance, imbibes considerably more water in the presence of small quantities of acids or acid salts, whereas lecithin takes up less water under the same circumstances. Larger amounts would tend to have a different effect, but in the living organism only the smaller ones are found. Proteins preponderate in most of the human organs and regulate the water distribution. In other organs, such as the brain and the nervous system, the abundance of lipoids causes them to differ from all other organs.

The electrolytes present in the cell contents are: Chlorides, phosphates, carbonates, nitrates (K-,Na-,NH_4-salts), in the form of neutral, acid and basic salts—acids and bases. They increase the quantity of the water imbibed by the proteins (Hofmeister,[2] Pauli [3]). Nonelectrolytes,

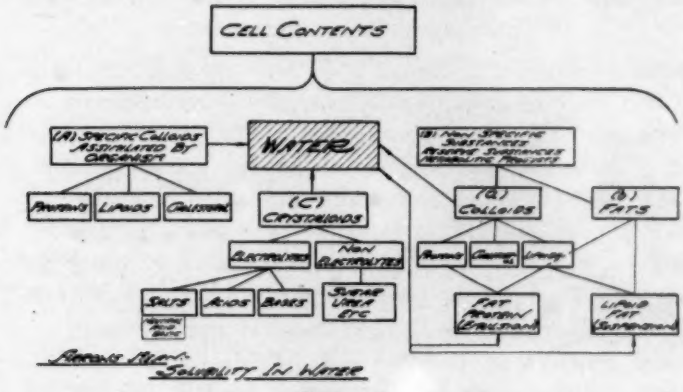

Figure 1.

such as sugar, urea, etc., as well as some salts of organic acids (acetate, citrate, tartrate), decrease this quantity.

The physicochemical process of water imbibition may be explained as follows: Chemical substances of low molecular weight are dissociated by water into their constituents (positive and negative ions). Chemical substances of high molecular weight form molecular complexes and are not dissociated by water, but adsorb water at the surface of their molecules or molecular complexes, "molecular imbibition" (Fick [1]). These substances are called "colloids." Colloids with smaller molecular complexes adsorb more water than those with larger ones; the first form emulsions, the latter suspensions. The water adsorbed by the molecular

2. Hofmeister, F.: Zur Lehre von der Wirkung der Salze, Arch. f. exper. Path. u. Pharmakol. **24**:1, 1888; **25**:1, 1889; **28**:210, 1891; Ztschr. f. physiol. Chem. **2**:299, 1878.

3. Pauli, W.: Untersuchungen ueber die physikalen Zustandsänderungen der Kolloide, Hofmeister's Beitr. z. chem. Physiol. **3**:225, 1903; **5**:27, 1904; **7**:531, 1906.

complexes is not available; it is "combined" water. Colloids forming emulsions adsorb more water than those forming suspensions. Splitting off of larger molecular complexes, for example, by a hydrolytic action is followed by a change of the colloid character; suspensions change to emulsions, emulsions change to solutions and finally to dissociated solutions. These changes go hand in hand with remarkable differences of the quantity of the combined water. The diminution of the molecular complexes of suspensions into emulsions is associated with an increase of combined water. The diminution of the molecular complexes of emulsions to crystalloids coincides with an increase of available water. Solutions are emulsions in a state of maximal imbibition. Gels are formed by suspensions under certain circumstances (as for instance at low temperature). The water imbibed by gels is closely combined with the molecular complex, just as the water of crystallization is a constituent part of the molecule of the crystalloid.

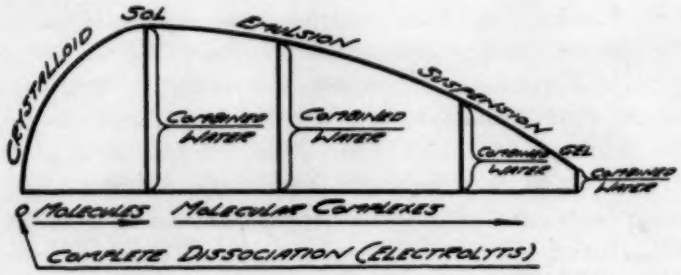

Figure 2.

PHYSIOLOGIC CONDITIONS FOR THE EQUILIBRIUM OF THE CELL CONTENTS IN LIVING CELLS

A. The static equilibrium of the cell contents is regulated by the colloidal nature of their constituents, mainly through the surface tension of their colloidal particles. There is a strife between these particles for water, but at the same time there exists a mutual protection ("protecting colloids") against products dissolved in this water, as an excess of salts, acids, bases and other substances; these substances would alter the colloid character of the cell protoplasm and the stability of the system.

B. In the dynamic equilibrium of the cell contents there is a continuous change of the quantity and quality of the constituents of the nonspecific reserve substances and metabolism products; they are caused by hydrolytic and synthetic processes, as we know by the very exact calculations of C. Voit.[4] The alteration of the molecular weight of

4. Voit, C.: Physiologie des allgemeinen Stoffwechsels und der Ernaehrung, in Herman, L.: Handbuch der Physiologie, 1883.

colloids by catabolic processes may be compensated by corresponding synthetic processes or by secretion of the surplus of the available water. In the cells of secretory glands, for instance, we may observe the process by means of the microscope. There is a continuous change of the quantity and the character of the crystalloids, which are partly excreted with the water and partly may be split into electrolytes with smaller molecules. Acid salts may change into neutral or basic salts and vice versa. The consequence is a mutual exchange of water and salt between the different colloidal constituents of the cell and between these and the intercellular lymph and blood capillaries.

PHYSIOLOGIC FORMATION OF WATER IN LIVING CELLS

As with other substances of the human body—uric acid, for instance—water is of a twofold origin: exogenous and endogenous water. The catabolic and anabolic processes which take place in the living body cells convert substances which are rich in hydrogen into substances with a lower content of this element: oxydation. The hydrogen ions combine with the oxygen, partly supplied either indirectly by the lungs or by food rich in oxygen (carbohydrates for instance), forming water: endogenous water. Endogenous water is water in statu nascendi, and has, like all chemical products in this stage, a higher activity, especially in hydrolytic catalytic processes. The quantity of water formed by the human organism during a complete withdrawal of food and water shows the average figure of 288 Gm. daily. This water production rises, if the individual has a normal diet and water supply, attaining an average value of 360 Gm. daily and a maximum of 468 Gm. if the diet is rich in fats. Sixteen per cent of the water excreted by the kidneys during one day is endogenous water, that is, water produced within the body cells.

INFLUENCES WHICH CAUSE AN INCREASE OF WATER IMBIBITION BY THE COLLOID SUBSTANCES OF LIVING CELLS

Influence of Increase of the Temperature on the Water Imbibition by Cell Colloids.—The amount of water taken up by the body cells at normal body temperature increases with the temperature within certain limits in cells rich in protein. This colloid absorbs more water at higher temperatures than at lower under conditions which may occur in the human body, that is, temperatures between 37 C. and 41 C. and the presence of monovalent salts in physiologic solutions (0.7-0.85 per cent NaCl). The water imbibition or "swelling" at higher temperatures is caused by a relaxation of the molecular complexes, a larger distance between the colloid particles, and a decrease of the surface tension.

The alteration of cells rich in lecithin and phosphatides (brain, nervous system) through an increase of the temperature within the limits mentioned may be similar, but needs further investigation.

Influence of Chemical Composition of Surrounding Medium.—(*a*) Changes of acidity and alkalinity are important for the quantity of water imbibed by living cells. They are limited and regulated by the presence of phosphates and carbonates acting as buffers. Within these limits a moderate decrease of the normal p_H rate as well as a moderate increase are both followed by an increase of water imbibition. This may be considered as an automatic protection of the cell protoplasm by dilution of the excess of hydrogen ions or hydroxyl ions which are both very active in producing hydrolytic changes.

(*b*) The quantity of crystalloids, the degree of their dissociation and their chemical value (monovalent-divalent) are closely connected with the changes in the water imbibition by the cell colloids. Formation of smaller, more dissociated molecules and retention of monovalent salts (Na-, K- salts) increase the quantity of water imbibed. Formation of larger molecules and retention or presence of bivalent salts (Ca- salts for instance) have the opposite effect.

PATHOLOGIC CONDITIONS FOR DISTRIBUTION OF WATER AND SALTS IN LIVING CELLS DURING FEVER

A. Effect of Fever on Water Distribution.—(1) The direct consequences of increased body temperature in different organs of the human body depend in the first place on the character of their colloids. The parenchymatous organs, the protoplasm of which is very rich in protein, imbibe more water at 40 C. than at 37 C., as mentioned above. The imbibition of water alters the conditions for the optic molecular refraction of certain protoplasmic parts, which become visible and are the cause of the "cloudy swelling." This imbibition of water may seem small for one cell, but it becomes a considerable amount if we imagine the total surface of one organ. The "total surface" of one organ is composed of all its cell surfaces. If we divide a cube the size of 1 cc. into smaller parts, so as to obtain cubes the size of 0.1, 0.01, 0.001 cc, the total surface increases in proportions of 1 : 1,000, 1 : 1,000,000 and 1 : 1,000,000,000. This will illustrate the immense quantity of water absorbed by the total surface of all parenchymatous organs.

Organs not as rich in protein as the parenchymatous tissues take up smaller quantities, or may even lose water (skin, subcutaneous tissue, mucous membranes, muscles), as will be explained later. The brain, containing the highest amount of water under normal conditions, shows other alterations. The gray substance of the brain contains 83.5 per cent,

and the white substance 70 per cent of water (Halliburton[5]). This is a state of almost maximum water imbibition, and the living cells of this tissue probably will not imbibe any more water, even if their temperatures should be increased. But these conditions have not been well studied as yet. The water imbibition by lecithin may be influenced by smaller amounts of salts than the water imbibition by albumin, as shown by the author in a previous article.[6] There are, for instance, different results obtained in working either with physiologic sodium chloride solution or with Ringer's solution (containing 0.00025 $CaCl_2$ in 1 cc.).

(2) There are also indirect consequences of fever: (*a*) Breaking down of proteins may be a consequence of fever or it may have the same causes: the presence of toxic substances in the blood. The large albumin complexes are transformed to polypeptids, albumoses and peptones, amino-acids and smaller molecules. The remaining albumins and colloids of the cell are enabled to absorb the surplus of available water by the increased quantity of electrolytes resulting from this transformation (Lillie[7]). (*b*) Another consequence of the fever is an alteration of the chemical reaction of the blood. According to Kraus,[8] the blood alkalinity is diminished during fever. Limbeck and Steindler[9] could not confirm the same fact as being true of all febrile processes. Strasser and Kuthy[10] found that by warm and hot baths the alkalinity of the blood was diminished while increased by cold. (Experiments were made on men and dogs.) Unfortunately, all these observations have been made by old methods (titration) and should be revised by more modern procedures (determination of the hydrogen ion concentration, that is, p_H). Michaelis and Rona,[11] as well as Henderson,[12] showed

5. Halliburton, W. D.: Die Biochemie der peripheren Nerven, Ergebn. d. Physiol. **4**:29, 1905; Ztschr. f. physiol. Chem., 1877-1881.

6. Pribram, E.: Die Bedeutung der Quellung und Entquellung für physiologische und pathologische Erscheinungen (Beitraege zu einer Physiologie der Zelle), Ztschr. f. Kolloidchemie **2**:1, 1910.

7. Lillie, R. S.: The Influence of Electrolytes and of Certain Other Conditions on the Osmotic Pressure of Colloidal Solutions, Am. J. Physiol. **20**:127, 1907.

8. Kraus, F.: Ueber die Alkalescenz des Blutes bei Krankheiten, Ztschr. f. Heilkunde **10**:2, 1889.

9. Limbeck and Steindler: Ueber die Alkalescenzabnahme des Blutes im Fieber, Centralbl. f. inn. Med., 1895.

10. Strasser and Kuthy: Ueber die Alkalinitaet des Blutes und die Aciditaet des Harns bei thermischen Einwirkungen, Blaetter f. klin. Hydrotherapie **6**:1, 1891.

11. Michaelis and Rona: Elektrochemische Alkalinitaetsmessungen an Blut und Serum, Biochem. Ztschr. **18**:317, 1909.

12. Henderson: Das Gleichgewicht zwischen Basen und Saeuren im tierischen Organismus, Asher-Spiro's Ergebn. d. Physiol. **8**:254, 1909.

that within the range of temperatures of 18 C. and 38.5 C. the concentration of hydrogen ions in a liquid of the composition of blood can rise only a little, whereas the alkalinity of the same fluid, measured at body temperature, may rise two or three times higher than that measured at 18 C. This alkalinity increases from 15 to 20 per cent if the temperature of the body rises to that of high fever, 42 C. Henderson [12] calculates that every moderately diluted solution of carbonic acid and sodium bicarbonate at 37.5 C. has an alkalinity about 3.3 times as high as at 18 C. 4 times at 42 C.; increasing its alkalinity amounts to 20 per cent if the temperature rises from 38 to 42 C. These changes in the concentration of the hydroxyl ions are due to the fact that the dissociation constant of water is higher than that of carbonic acid (weak acid). Henderson's [12] researches with blood of pigs and those of Michaelis and Rona [11] with blood of dogs showed the same phenomenon; by increasing the temperature from 20 C. to 39 C. the concentration of hydrogen ions remained almost constant, while the concentration of the hydroxyl ions was very much increased. Living tissue cells are very sensitive to a rise of the hydroxyl ion concentration of the surrounding medium, as will be shown in a further publication. A remarkable swelling due to water absorption has been observed.

B. Effect of Fever on the Salt Distribution.—(1) Sodium chloride: with the imbibing of water the swelling colloid will also absorb salts. In this process almost proportionately, sometimes relatively, more salts than water is absorbed. The salt that is absorbed mainly in the tissues with the increase of the temperature is sodium chloride. A decrease in the absolute quantity of sodium chloride of the urine is found, which in high fever can be reduced to a minimum (Salkowski [13]).

(2) Potassium Salts: Contrary to the diminished secretion of sodium salts during the fever, the secretion of potassium salts by the kidneys is increased. It is usually three or four times as large as normally and may be seven times as large in extreme cases (Salkowski [13]). We can trace the potassium by determining the entire molecule; it has been found as phosphoric salt. In this combination it is contained in the muscles. The release of potassium salts by the muscles may be in close relation to the exchange of water between these and other organs during high body temperature. The imbibition of muscles with water shows a close analogy to the imbibition of soaps with water; soaps containing potassium can be dissolved very easily, soaps containing sodium much less so. Similarly, a muscle imbibes more or less water according to its being brought into isosmotic solutions of either potassium chloride or sodium chloride, in which it remains for a certain time

13. Salkowski, E.: Untersuchungen ueber die Ausscheidungen der Alkalisalze, Virchows Arch. f. d. ges. Physiol. **53**:209, 1871.

(Loeb [14]). The muscle cell of the normal organism is rich in potassium salts. The intercellular substance is rich in sodium salts. During the increase of the body temperature caused by febrile processes, the muscle releases potassium salts as illustrated by the appearance of potassium salts in the urine. Its capacity for swelling decreases and its water contents [15] become available for other organs. Therefore we have here an important fact regulating the fluid current from the muscle tissue to the inner organs.

REGULATION OF DISTRIBUTION OF WATER IN DIFFERENT ORGANS DURING FEVER COMPARED WITH REGULATION DURING CUTANEOUS TEMPERATURE CHANGES

Barbour and Hamilton [16] and Barbour, Dawson and Neuwirth [17] studied the water regulation of the body in cold and in warm environment. It will be of interest to compare these conditions with the conditions during the fever, that is, during a general increase of temperature of all parts of the body. Barbour and his collaborators found that in a cold environment, through loss of water, the blood becomes anhydremic. The fluid which leaves the blood is directed chiefly to the cold skin, subcutaneous tissue and muscles. On exposure to a warm environment, water and salts enter the blood plasm in such a way as to result in hydremia. During fever, as we have seen, the fluid is diverted from the skin, the subcutaneous tissue and from the muscles, as well as from the blood, to the inner organs. We find the same direction of flow in all cases of heavy loss of water, as cholera asiatica, cholera infantum. There is a lack of water in the parenchymatous organs in these (nonfebrile) diseases too, because they are losing their normal water contents. The regulation is the same. There has been found an increase of the potassium salts in the urine, having doubtless the same origin as in febrile diseases, namely, the muscle tissue.

The different reaction of the peripheral and central organs to the same irritation is not limited to their physical and chemical qualities alone. As we know by recent articles of Mueller and Petersen,[18] the

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14. Loeb, J.: Ueber die Aehnlichkeit der Fluessigkeitsresorption in Muskeln und Seifen, Pflueger's Arch. f. d. ges. Physiol. **75**:303, 1899.

15. The muscles, being 42.82 per cent of the body tissue, contain 47.74 per cent of the water of the human body.

16. Barbour and Hamilton: Heat Regulation and Water Exchange, Am. J. Physiol. **73**:315, 665, 1925.

17. Barbour, Dawson, and Neuwirth: Heat Regulation and Water Exchange, Am. J. Physiol. **74**:204, 1925.

18. Mueller, E. F., and Petersen, W. F.: Ueber das splanchnoperiphere Gleichgewicht der Gefaesspermeabilitaet und seine klinische Bedeutung, Klin. Wchnschr. **5**:53, 1926.

skin belongs to the parasympathetic and the inner organs to the sympathetic nervous system. These two systems are antagonistic, and it is probable that they take part in the regulation of the water supply by the skin.

CLINICAL CONSEQUENCES OF LACK OF WATER DURING FEVER; TREATMENT

The clinical consequences of the lack of water during fever are: dryness of skin, thirst, and diminished renal secretion; the opposite: perspiration and abundance of renal secretion as observed during the decrease of the fever. These symptoms were objects of observation by experienced physicians long ago; nevertheless no satisfactory explanations were given until now. Only those clinical cases can be used for the discussion of this question in which the renal function is normal. The "state of thirst" of the organism is caused, as explained, by the lack of water in the inner organs, which attract the available water from the periphery. Sometimes a moderate rise of temperature, 1 to 2 degrees, is sufficient to cause retention of a great deal of water, several liters, in fact, if a large quantity is available. In a former paper, I [19] described the observations in ten cases of diabetes insipidus. One of these patients became ill with influenza, with a rise of the body temperature of 1 to 2 C., causing the amount of urine to diminish from 6,500 cc. to 2,300 cc. The author observed the same symptoms in two other cases of a mild diabetes insipidus, in which the amount of urine fell from 3,300 cc. to 1,900 cc., from 2,500 cc. to 1,700 cc., respectively, in consequence of intercurrent rise of temperature. This same observation was made long ago (1871) by A. Pribram [20] in three cases of diabetes insipidus during a febrile bronchitis, an iritis and again during an exanthematic fever.

The result of our discussions for the treatment of continual fever is to recommend an abundant supply of water. We find in the literature an empiric treatment for typhoid fever recommended by two different authors: Sahli [21] and Valentini [22]: "Two liters of milk, one liter of

19. Pribram, E.: Klinische Beobachtungen bei 10 Faellen von Diabetes insipidus, Deutsch. Arch. f. klin. Med. **76**:197, 1903.

20. Pribram, A.: Prager Vierteljahrschrift f. praktische Heilkunde **28**, 1871.

21. Sahli: Ueber die Auswaschung des menschlichen Organismus und über den Wert und die Methoden der Wasserzufuhr bei Krankheiten, Cor.-Bl. f. Schweiz. Aerzte **20**:17, 1890.

22. Valentini: Ueber die Methode und Wirksamkeit grosser Wasserzufuhr bei Infektionskrankheiten, vorzueglich bei Typhus, Deutsche med. Wchnschr. **17**:914, 1891.

soup and a certain amount of water every day, so that the daily quantity of urine may rise from 500-600 cc. to 5,000-6,000 cc."

SUMMARY

During fever the human organism is in a state of thirst. This state of thirst is caused by a change of the distribution of water in the organism. The parenchymatous organs absorb more water owing to their contents of protein. The causes of the increased demand of water by the parenchymatous organs are of physiochemical nature. The rise of the temperature, the breaking down of proteins and the change of the chemical reaction of the blood (increase of hydroxyl ions) all produce the same effect, an increased faculty of the cell colloids to imbibe water.

Proteins take up more water if the temperature rises from 37 C. to 40 C. Organs not so rich in proteins (the skin, the mucous membranes, the subcutaneous tissue) and the muscles lose water, supplying the inner organs with water. The delivery of water by the muscles may be explained by an exchange of their potassium salts for sodium salts. We find an increase of the quantity of potassium phosphate in the urine and a decrease of sodium chloride. The origin of the potassium salts is doubtless the muscle tissue. This tissue has the faculty of imbibing more water in the presence of potassium salts than in the presence of sodium salts. The loss of water by the skin, the mucous membranes and the subcutaneous tissue cannot yet be explained in a similar manner, but recent articles (Mueller and Petersen [18]) make it probable that there the nervous system (parasympathetic system) exerts a regulating influence.

GANGLIOGLIOMA *

ORMAN C. PERKINS, A.M., M.D.
BROOKLYN

During the past fifteen years the interest in tumors of the nervous system has increased, although it has been recognized for a much longer time that nerve tissue may undergo blastomatous change. Nerve tumors consisting of nerve tissue elements may form in any part of the nervous system, although the largest number reported have their origin in the sympathetic system.

Neuroma was first described by Odier [1] in 1803, but this term was applied to swellings occurring along peripheral nerves, regardless of the type of tissue which formed the tumor. Virchow,[2] 1863, studied the histologic structure of these swellings and brought about a classification of true and false neuromas and a still further subdivision into: (1) neuroma gangliocellulare; (2) neuroma fibrillare amyelinicum; (3) neuroma fibrillare myelinicum.

Beginning with Loretz [3] in 1870, who described the first authenticated case of ganglioneuroma, there have been numerous cases reported by various workers (Keys,[4] 1879, Weichselbaum,[5] 1881, Busse [6] and Borst,[7] 1897, Chiari [8] and Knauss, 1898, Beneke,[9] 1901).

The first neuroma of the central nervous system was described by Worcester [10] in 1901. He believed that the cells had arisen from small round cells of an indifferent character which might develop into either nerve cells or glial cells. Schminke,[11] in 1910, described nests of young cells having the appearance of neurocytes grouped about vessels ("Bildungsnester," "Proliferationszentern"). He described various transitions from sheath cells to nerve fibers, and noted the presence of young nerve forming tissue as seen in syncytial neuroblastic masses. He believed that this tumor originated as a cell "rest" separated from the cerebrum during fetal life. Pick and Bielschowski,[12] in 1911, intro-

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* From the Departments of Anatomy and Neurology, Long Island College Hospital.

1. Odier, quoted by Wohl: J. M. Res. **30**:205, 1914.
2. Virchow: Die Krankhaften Geschwulste **2**:150, 1864.
3. Loretz: Virchows Arch. f. path. Anat. **49**, p. 435.
4. Keys, quoted by Wohl.
5. Weichselbaum: Virchows Arch. f. path. Anat. **85**:554, 1881.
6. Busse: Virchows Arch. f. path. Anat., Suppl. **151**, p. 66.
7. Borst: Sitzungsbericht d. physilck med. Gesellsch., Wurzberg, 1897.
8. Chiari: Verhandl. d. Naturforscherversammlungen, Dusseldorf.
9. Beneke: Beitr. z. path. Anat. u. z. allg. Pathol. **30**: 1901.
10. Worcester: J. M. Res. **1**:59, 1899.
11. Schminke: Virchows Arch. f. path. Anat. **41**:267, 1910.
12. Pick and Bielschowski: Berl. klin. Wchnschr. 1913, nos. 1 and 2, p. 16.

duced a new classification of true neuromas. This classification was based on the theory that all true neuromas have their origin in displacements or malformations of neurocytes and that the type depends on the extent of differentiation.

Marchand,[13] in 1891, described a neuroblastoma of the undifferentiated type found in the medulla of the suprarenal gland. Other tumors of this type were reported by Kuster,[14] in 1905, Wright,[15] in 1910, and others. A third type of tumor was described by Hedinger [16] in 1909, originating from the paraganglioma. This last type is a chromaffine tumor or paraganglioma. Others of this group have been described by Zuzuki [17] in 1910 and Kawashima [18] in 1911. Wohl,[1] in 1914, described an interesting case in which there were two forms of cell elements. One form was highly differentiated, while the other represented the embryonic nerve cell. This is called a ganglioneuroma, and was believed to have developed from sympathetic nerve cells.

The more one investigates the literature, the more confused he becomes as to the classification of the neurogenic growths. There seems to be a consistent agreement in regard to the genetic relationships of neurocytoma (Marchand) and neuroblastoma. The neurocytoma represents the undifferentiated type in which the primal neurocyte of the ectoderm has undergone a metamorphosis through stages in which the nucleus enlarges and becomes more diffuse in its staining; the cytoplasm also increases, acquiring at the same time a more or less peculiar arrangement, and the growth of fibrils occurs. The neuroblastoma represents the differentiated type which may contain both mature and immature nerve cell elements. This type is most often found associated with the sympathetic system and has been called sympathoblastoma. A third group is isolated because of its association with the sympathetic nervous system and also the affinity that its cells have for chrome salts. These are called paraganglioma (Zuzuki) or phaeochromocytoma (Poll [19]). A fourth group, ganglioneuroma, in which the cell elements are of the highest specialized type, can be identified as mature ganglion cells.

In the case to be presented in this article, a tumor of the brain was found which we find difficulty in placing under any of the various types heretofore mentioned. Because of its peculiar histologic make-up, as well as the infrequency of these tumors in general, we feel that such a case should be placed on record in the literature.

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13. Marchand: Festschrift f. Virchows Internat. Beitr. zur Wissensch. med., 1891, p. 1; Festschrift f. Rindfleisch, 1907.
14. Kuster: Virchows Arch. f. path. Anat. **180,** 1905.
15. Wright, J. H.: J. Exper. Med. **12:**556, 1910.
16. Hedinger: Frankfurter Ztschr. f. Path. **7,** 1909.
17. Zuzuki: Berl. klin. Wchnschr. **36:**1644, 1909; **35,** 1910.
18. Kawashima: Virchows Arch. f. path. Anat. **203.**
19. Pol: Hertwig's Handbuch d. Entwickelungsgesch.

REPORT OF A CASE

History.—A., aged 16, was brought into the hospital complaining of headaches, vomiting and drowsiness. The family history was negative. He began school at 7 and continued up to 15½ years. During this time, he progressed rapidly in his school work. No evidence of mental deficiency or abnormalities of any kind was observed by his family. He had always been well up to the time of the present illness.

The patient's illness began two and one-half weeks previous to the date of admission, when he complained of headache and blurred vision. On the second day of his illness, he vomited without any apparent cause, and no nausea preceded the vomiting, which was projectile in character. Although he continued at his

Fig. 1.—Portion of tumor protruding through the floor of the third ventricle, forcing the lateral walls of the ventricle apart and acting as a ball-valve at the entrance of the iter.

work for the following four days, his condition gradually grew worse. These headaches became severe and more marked in the occipital region; his vision became impaired, and he felt dull pain in his eyes. He could not see the signs on the cards which he handled at his work; neither could he see the signs on the trolley cars, and he was obliged to walk home from work. He vomited regularly every other day without any cause and not related to food. On the fifth day of his illness he was obliged to go to bed. He became very drowsy and slept most of the time, but could be aroused; he would wake up for his meals and fall asleep again as soon as he had finished eating. His appetite was good. Constipation set in and pecame persistent.

His condition became worse, and he finally became very weak. On the day before admission, while attempting to walk to the bathroom, he fell and could not

get up. He had to be helped to his bed. He lost considerable weight during this illness, but just how much he did not know. There was no history of convulsions or diplopia. He was brought to the hospital in a semistuporous condition.

Physical Examination.—This revealed a youth, well nourished, semiconscious, but who could be aroused for a short time. There seemed to be some paresis of the fourth and sixth cranial nerves on the right side. There was also a lagging of the muscles of expression on the right side of the face. The pupils reacted to light and in accommodation.

The lungs were normal. The cardiac impulse was diffuse, wavy and had a peculiar double roll. The apex beat was localized in the fourth interspace 0.5 cm. outside the nipple line. The first sound at the apex was low pitched accompanied by a soft systolic blow not well transmitted. The second sound was clear. The systolic murmur was heard at the tricuspid area, as well as at the pulmonary area. The second pulmonic sound was greater than the second aortic. A diastolic murmur was heard at the base.

The abdomen was normal. The right patellar reflex was increased over the left. There was a Babinski sign on the right side. The temperature was 99 F., the pulse rate 77, respirations 24; blood pressure, 130 systolic and 78 diastolic. Lumbar puncture revealed 40 cc. of clear fluid under moderate pressure. The cell count was 200, and Benedict's solution was not reduced; there was a slight reaction for globulin. Cell count showed 70 per cent of lymphocytes, 30 per cent of polymorphonuclear leukocytes. The colloidal gold and Wassermann tests were negative. The blood Wassermann test was negative. Examination of the blood revealed: red blood cells, 4,600,000; white blood cells, 18,000; hemoglobin, 88 per cent; differential count: polymorphonuclears, 72 per cent; lymphocytes, 24 per cent; eosinophils, 2 per cent; transitionals, 2 per cent.

The patient died on the second day after admission.

Necropsy.—The dorsal view of the brain showed nothing abnormal except six or eight small pinhead elevations on the pia, which at first glance would be taken for tubercles. On microscopic examination, these proved to be only thickened portions of the pia with no evidence of inflammation. The ventral surface showed the mammillary bodies crowded out into the interpeduncular space. On opening the corpus callosum, there was a tumor protruding through the floor of the third ventricle, 3 cm. in width, 4 cm. in length and 2.5 cm. in height. It was purplish, very firm and hard. The lateral ventricles were distended by the blockage of the cerebrospinal fluid at the entrance of the iter, the tumor acting as a ball valve, producing internal hydrocephalus.

On dissection, the tumor mass was found to extend into the tegmentum of the brain stem, involving the anterior portion of the red nucleus on each side and passing ventrally through the substantia nigra and even encroaching on the cerebral peduncles. The tumor was removed and fixed in Orth's fluid. The sections were stained in hematoxylin and eosin as well as in Nissl's stain. It was found necessary to decalcify portions of the tumor, as in the dorsal half there were large calcified areas.

Examination of the slides showed a tumor made up of islands of large cells, the islands separated by considerable fibrous-like tissue. The cells varied in size from 8 to 10 microns up to 40 microns in the multinuclear types. Many of the cells contained two nuclei, but the largest of these giant cells contained as many as eight or nine. There was no evidence of indirect division in any of the tumor cells. These large cells occurred in groups, each group separated from its neighbors by fibrous-like tissue. In these cell knots there was considerable activity in direct cell division, as shown by the predominance of multinuclear cells. The

isolated cells found in the fibrous-like tissue among the knots were more regular in outline, more uniform in size and contained as a rule a single nucleus. The latter cells had a tendency to be spindle shaped, with two processes which could be traced for some distance even with the Nissl stain.

The nucleus was of the vesicular type, having a well defined membrane and varying in size and in shape to correspond to the size and the shape of its cell body.

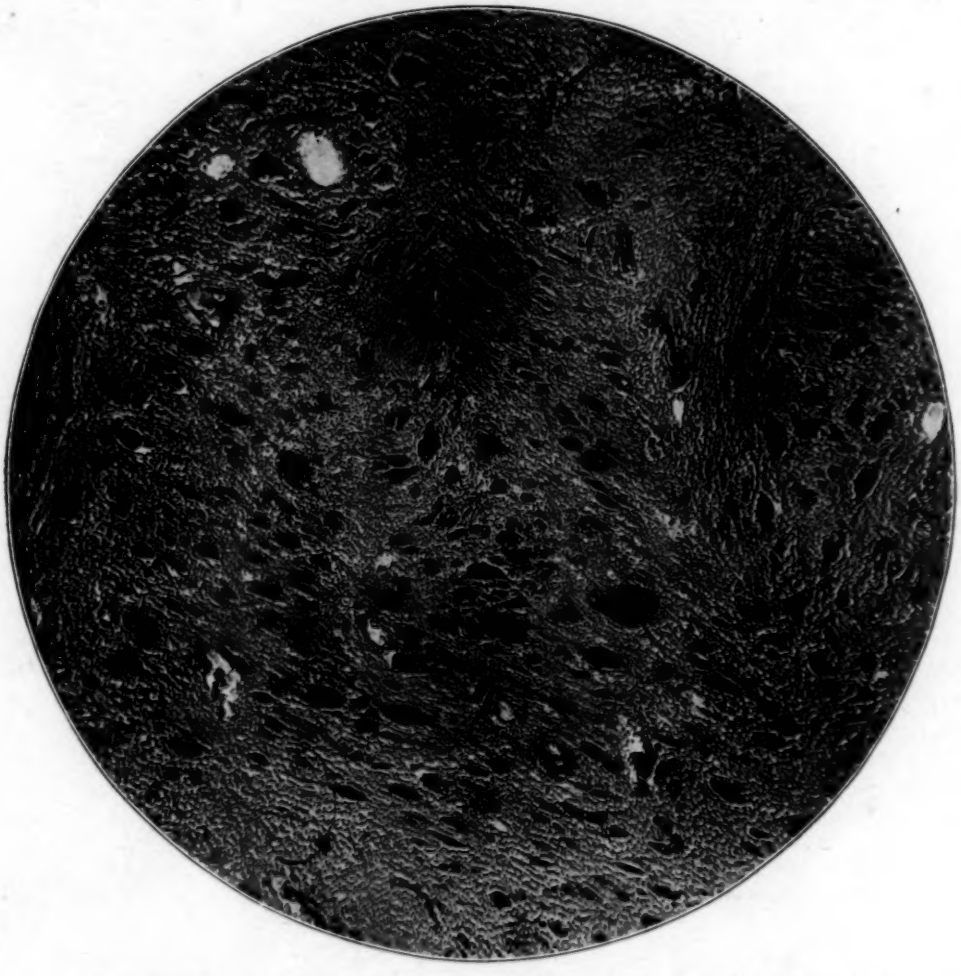

Fig. 2.—Fibrous matrix of the tumor containing ganglion cells of the simple type as well as the multinuclear giant cells; reduced from a magnification of × 150.

There were many deep staining chromatin knots along the network. Two nucleoli were present in a few of the nuclei.

The cells in the island showed many chromophilic granules. The granules varied in size and in distribution. There was a tendency for the large granules to be arranged in rows beneath the cell membrane, as in the perichrome cells of the substantia gelatinosa. The other cells presented no specific arrangement of

these granules and had the appearance of the gryocome cells as seen in the root ganglions of the cranial nerves. These granules were not found in as great abundance in those cells isolated in the matrix. The granules extended for a short distance into the bases of the large processes. In the islands the concavities between the processes of the cells were clearly made out, and the number of processes varied from two to eight or ten. Many of the processes of the largest cells had wide bases, while those of the smaller cells had narrow bases.

Fig. 3.—Simple ganglion cells and multinucleated giant cells in the fibrous matrix; reduced from a magnification of × 230.

There was great cell activity in the upper pole of the tumor, the portion that protruded through the floor of the third ventricle. In the upper third of the tumor were many calcified areas. There was no evidence of cystic degeneration. The entire tumor showed many well formed blood vessels.

The matrix of this tumor formed a large part of the tissue mass. It was characterized by the large amount of fibrous-like tissue and lack of cellular

elements. The fibers took a deep eosin stain, but there was no evidence of collaginous tissue in any part of the matrix as shown by the van Gieson stain. There were no elastic fibers found with the Verhoeff elastic tissue stain. The processes of the ganglion cells are unmyelinated in this matrix as no myelinated fibers could be found when stained by the Pall-Weigert method. There was no reaction of any of these fibers to the glial stain. It is hard to explain just what this matrix represents. It resembled neuroglial tissue, and it is possible that the specificity for this stain had not developed; that is, these fibers may be embryonic neuroglial fibers or young connective tissue fibrillae.

Dark staining cells were scattered throughout the matrix. These cells were difficult to identify. They may represent undifferentiated nerve cells, but I believe they are more likely to be neuroglia cells.

SUMMARY

In this article a tumor of the brain is recorded which, if described hitherto, is extremely rare. The name ganglioglioma is suggested for this tumor because of its richness in mature neurons embedded in a heavy matrix of fibrous-like tissue. The neurons showed great activity, dividing by amitosis. The matrix was abundant, and because of its nonspecificity for differential stains, it is believed to be of glial origin.

I wish to express my appreciation to Professor James Ewing, Cornell University, for suggesting that the name ganglioglioma be applied to this tumor, and for the valued counsel and assistance rendered during the progress of the work.

STUDIES IN THE PATHOLOGIC ANATOMY OF THE HYPOPHYSIS

IV. NECROSIS AND ATROPHY *

J. P. SIMONDS
AND
W. W. BRANDES
CHICAGO

Many acute lesions of the hypophysis are associated with fatal diseases of other organs of the body. Hence in the case of many interesting pathologic processes in this small gland, it is often impossible to determine their effect on its function, partly because any symptoms induced by the lesion itself are obscured by the more serious disease from which the patient is suffering, and partly because the patient does not survive long enough for any chronic effects of hypophysial disorder to manifest themselves. It is with these considerations in mind that four cases of localized necrosis and atrophy of the anterior lobe of the hypophysis are here reported.

Thaon [1] found a very small necrotic patch in the hypophysis of a tuberculous patient. Berblinger [2] saw anemic necrosis of the hypophysis in eclampsia, and hemorrhagic infarction of the anterior lobe in a case of thrombosis of the sinus circularis. Schmorl [3] mentioned two cases of localized necrosis of the hypophysis in eclampsia, two due to bland infarcts, and stated that hemorrhagic necrosis can follow trauma, especially fracture of the skull. Anemic infarction of about one-half of the posterior lobe and between seven-eighths and nine-tenths of the anterior lobe in a patient with verrucose endocarditis has been observed by Merkel.[4] Glinski [5] made a brief reference to two instances of necrosis in the hypophysis, one in a woman who died of a general pyemia, and another in a woman who died of "heart failure" six weeks after an abortion. Of thirty-five cases of pyemia, Plaut [6] found the hypophysis affected seventeen times. Necrosis was one of the changes seen in the anterior lobe. Simmonds [7] has stated that embolic

* From the Department of Pathology, Northwestern University Medical School.

1. Thaon: L'hypophyse a l'etat normale et dans les maladies, Paris, 1907.
2. Berblinger: Verhandl. d. deutsch. path. Gesellsch. **17,** 1914.
3. Schmorl: Verhandl. d. deutsch. path. Gesellsch. **17:**231, 1914.
4. Merkel: Verhandl. d. deutsch. path. Gesellsch. **17:**193, 1914.
5. Glinski: Deutsche med. Wchnschr. **39:**473, 1913.
6. Plaut: Klin. Wchnschr. **1:**552, 1922.
7. Simmonds, M.: Virchows Arch. f. path. Anat. **214:**226, 1914.

processes in the hypophysis are not rare and has reported four cases associated with septicemia, similar in essential respects to the first two cases in our series. Plaut [8] has given brief descriptions of hypophyses showing necrosis in three patients, two of whom had a purulent meningitis, the other a septicemia following abortion.

A brief summary of our cases follows.

REPORT OF CASES

CASE 1.—A boy, aged 13, had bilateral purulent otitis media and mastoiditis with complicating purulent leptomeningitis. Necropsy was limited to the head and confirmed the clinical diagnosis.

The hypophysis was slightly enlarged. In one lateral half of the anterior lobe was a sharply demarcated area of coagulation necrosis measuring approximately 4 by 6 mm. (fig. 1). Its borders were scalloped and composed of necrotic acini separated from normal glandular tissue by very narrow connective tissue trabeculae. There was little or no reaction either in the form of round cell infiltration or hyperemia in the tissues immediately surrounding the necrotic portion. Within the area all of the epithelial cells had undergone complete coagulation necrosis; their nuclei did not stain and their cytoplasm stained deeply with eosin. Some of the cells were beginning to disintegrate. In the necrotic area an occasional connective tissue cell with a pyknotic nucleus was seen. At about the center of the mass there was an accumulation of polymorphonuclear leukocytes. No thrombus could be found in any of the vessels of this hypophysis, which was cut in interrupted serial sections. The capsule was infiltrated with polymorphonuclear leukocytes. In the anterior portion of the glandular part, but in a different plane from that of the region of necrosis, there was a subscapular abscess.

CASE 2.—Necropsy of a well nourished white woman, aged 62, showed lobar pneumonia, fibrinopurulent pericarditis and pleurisy (bilateral), beginning chronic diffuse nephritis and cloudy swelling of the heart and liver.

The hypophysis was of normal size. In one lateral half of the anterior lobe there was a mass somewhat more than 1 mm. in diameter, in which the epithelial cells were in a condition of coagulation necrosis. The connective tissue framework was still visible, and its nuclei stained fairly well. In the trabeculae the blood vessels were collapsed and free from blood. No thrombus was seen in any vessel in or near the area of necrosis. One vessel in the plexus in the central core of connective tissue was thrombosed, but it seems doubtful whether this was concerned with the patch of necrosis.

CASE 3.—Necropsy of a well nourished colored woman, aged 39, showed lobar pneumonia complicated by pneumococcus meningitis, acute ulcerative aortic endocarditis and acute glomerulonephritis.

The hypophysis was about normal in size. In the anterior lobe there were four isolated, rather sharply demarcated areas in which the capillaries were markedly distended with blood, and the epithelial cells were few and small, and often had pyknotic nuclei. The trabeculae of connective tissue were unchanged.

CASE 4.—Necropsy of a well nourished white woman, aged 45, revealed a glioma of the left frontal lobe of the brain, chronic nephritis and a moderately recent decompression trephine opening in the skull.

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8. Plaut: Virchows Arch. f. path. Anat. **237**:165, 1922.

The hypophysis was about normal in its horizontal diameters but was flattened. Just beneath the capsule on each side of the anterior lobe there was a crescent-shaped area in which the epithelial cells had almost completely disappeared (fig. 2). The blood vessels in these areas were widely dilated and filled with blood. The delicate connective tissue framework was distinctly visible and apparently unchanged. The few remaining epithelial cells in the affected area were small and round and resembled lymphocytes in size and in the character of their cytoplasm. Near the center of the anterior lobe was a single sharply circumscribed small area of coagulation necrosis. No thrombus was seen in any vessel.

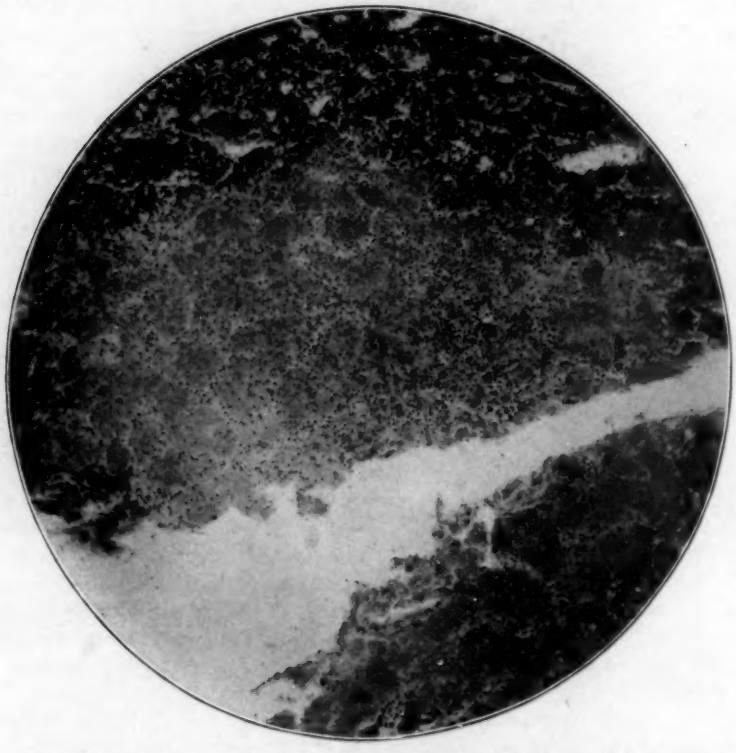

Fig. 1.—Area of necrosis in anterior lobe in case 1; × 60.

COMMENT

These four cases fall into two groups. In cases 1, 2 and 4 there was a localized area of coagulation necrosis in the anterior lobe. The necrotic patch in each instance was oval, sharply demarcated, and separated from the capsule by a zone of normal glandular tissue. In neither case was there any reaction in the form of round cell infiltration, edema or hyperemia in the adjacent healthy tissues. In case 1, the central part of the necrotic mass showed an accumulation of polymorphonuclear leukocytes. Careful examination of blood vessels in and about the areas of necrosis failed to reveal evidence of embolism

or thrombosis. Both patients suffered from an acute infectious disease, one a pneumonia complicated by a fibrinopurulent pericarditis and pleurisy, and the other from suppurative meningitis secondary to purulent otitis media and mastoiditis. In the latter case, none of the dural sinuses were thrombosed. Two of Plaut's cases were associated with purulent leptomeningitis. Case 2 did not show any vegetations on the heart valves. In case 4, there was no evidence of serious acute infection in any organ of the body.

Fig. 2.—Area of atrophy of the parenchyma of the anterior lobe in case 4. The connective tissue is not so much increased in amount as condensed as a result of loss of parenchyma. Some of the dilated blood spaces are visible; × 120.

Simmonds [7] has stated that the arteries of the anterior lobe of the hypophysis are functional end arteries, and that their occlusion may lead to infarction. In his cases the area of necrosis was wedge shaped, with its base at the capsule. It is probable that the lesions in our cases 1 and 2 were infarcts, but they differ from ordinary infarcts in being separated from the capsule by a zone of normal glandular tissue. This may be due to a special blood supply from vessels in the capsule to the subcapsular part of the anterior lobe.

Cases 3 and 4 were of a different type, and no reports of similar cases have been found in the literature. In these cases the parenchymal cells had more or less completely disappeared from certain rather sharply circumscribed areas, leaving the supporting tissue and vessels intact, the latter being markedly dilated. The location of these areas was constant, namely, laterally and somewhat superficially in the anterior lobe. There was nothing in the clinical histories or in the associated pathologic condition in either of these two cases that give a definite clue to the etiology of this lesion. Both patients were in middle life; neither showed any notable degree of arteriosclerosis; one died of meningitis complicating pneumonia, the other from tumor of the brain. It is possible that increased intracranial pressure may have been concerned in producing the lesion in the hypophysis.

If a patient with a pathologic process such as those described above should survive, it seems likely that the final results would be different in the two groups of cases. In the second group the connective tissue and vessels remained intact. With such a supporting framework to serve as a guide, it is not impossible that, once the cause is removed, the epithelium might be regenerated and the normal histologic architecture restored as in the case of the liver in nonfatal cases of acute yellow atrophy and chloroform poisoning. In the first group, however, with the parenchyma and stroma completely necrotic in the involved area, repair would result in a replacement by scar tissue. Simmonds has described a case in which he believed that a localized mass of fibrous tissue in the periphery of the anterior lobe had such an origin. Cases of the type of group 1, therefore, are of importance as the permanent destruction of a sufficient amount of the anterior lobe may lead to such deficiency of function as to cause changes in metabolism or other bodily functions definitely due to that cause. However, marked atrophy or replacement fibrosis of the anterior lobe of the hypophysis may occur without giving rise to noticeable symptoms during life. Krumbhaar,[9] among others, has mentioned such a case.

SUMMARY

Two groups of lesions in the anterior lobe of the hypophysis of patients dying from acute infections and brain tumor are described: (1) localized areas of necrosis in which parenchyma, connective tissue and blood vessels are completely destroyed, probably as a result of infarction; and (2) multiple localized areas in which the epithelial cells have completely or almost completely disappeared, leaving intact connective tissue and greatly dilated blood vessels.

9. Krumbhaar: M. Clin. N. Amer. **5**:927, 1921 (fig. 17); Arch. Diagnosis **14**:213, 1922 (fig. 14).

LEUKEMIA AND THE CENTRAL NERVOUS SYSTEM

WITH A REVIEW OF THIRTY CASES FROM THE LITERATURE

B. M. FRIED, M.D.

BOSTON

The neuropathologist is concerned with diseases which primarily involve the nervous system as well as with those which originate elsewhere and are prone to set up secondary complications therein. Among such diseases pernicious anemia is an outstanding example, owing to the frequency with which a lesion of the cord occurs. Indeed a spinal degeneration (funicular myelosis) is found in more than 80 per cent of studied cases;[1] and recently lesions in the brain in this disease analogous to those found in the cord have been described.[2]

In other hemopoietic or lymphopoietic disorders, comparable studies of the central nervous system have been largely neglected. The literature abounds with necropsy records of cases of leukemia, and yet only thirty cases have been found in which the investigation of the nervous system was ever reported. Two of these cases were reported by American, one by a British, one by a French and the others by German authors.

In the case herein reported the examination of the brain was purely accidental, and the spinal cord was not even examined. The gross observations therefore were entirely unexpected, and led to this study.

PERSONAL OBSERVATION

History.—A white man, American born, aged 25, unmarried, a radio tester, entered the Peter Bent Brigham Hospital, March 27, 1925, complaining of bleeding from the gums and nose. His family history was unimportant.

The patient had had measles at the age of 4, diphtheria and scarlet fever at the age of 5. In 1912, he had chills and fever daily for a week and thinks that he had malaria, but he had no medication and did not consult a physician. He spent a week in a hospital in 1918 with bronchitis and pleurisy. His tonsils and adenoids were removed at the Boston City Hospital in 1913.

His present illness began nine months before he entered the hospital, with malaise, weakness and a peculiar fluttering sensation over the region of his heart, more noticeable just after he had retired. After a brief rest these symptoms subsided, and he felt well for the next four months. Four months ago the

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* From the Surgical and the Pathological Laboratories of the Peter Bent Brigham Hospital.

1. Woltmann, H. W.: The Nervous System in Pernicious Anemia. An Analysis of 150 Cases, Collected Papers of the Mayo Clinic **1**:933, 1919.

2. Weimann, W.: Grosshirn Veränderung bei Anämie, Ztschr. f. Neurol. u. Psychiat. **92**:433, 1924.

same symptoms reappeared. He came to the outpatient department, where he was found to have a marked tremor, a heart enlarged to the left, and a systolic precordial murmur widely transmitted. His basal metabolic rate was plus 15.

For a month he had felt weak and tired, and one week ago he began to bleed from the gums. He recently had a dull throbbing headache over his frontal and parietal regions. Two days ago he had a nosebleed which came on suddenly without trauma. He consequently was admitted to the hospital.

Examination.—On admission examination showed a rather marked pallor, pale and bleeding gums, generalized glandular enlargement, a slightly enlarged spleen and many petechial spots over both arms and legs and neck. There were also small retinal hemorrhages. His white cell count was 640,000 per cubic millimeter. His differential count showed 88 per cent lymphocytes. The hemoglobin was 32 per cent. The erythrocyte count was 2,320,000 per cubic millimeter. The proportion of white to red cells was 1:3. His blood pressure was 114 systolic and 58 diastolic. The urine showed a slight trace of albumin, with few red cells and casts.

The day following his admission he complained of a moderate headache, and began to vomit thin bloody fluid without food particles. He became disoriented and moderately delirious, and died on the third day after admission in deep coma with a temperature of 105.5 F. (40.2 C.).

Necropsy.—Leukemic lymphadenosis. Apoplexy. Lymphomas of the central nervous system. Cutaneous petechiae. Fatty infiltration of heart and liver.

The body was that of a well developed and fairly well nourished white man. The skin had a yellowish tinge, and, particularly over the legs and arms, was dotted with numerous minute petechial hemorrhages. A few inguinal lymph nodes were present, the largest of which measured 0.5 cm. in diameter. A single mesenteric lymph node measuring about 2 cm. in diameter was also noted, and in the anterior mediastinum were two enlarged nodes, measuring 4 cm. and 3 cm., respectively. These were obviously lymphomas. They were creamy yellow, showing hemorrhages and necrosis.

The spleen was only slightly enlarged, weighing 225 Gm. It was normal in shape, firm in consistency and grayish, with a few localized opaque grayish-white thickenings. The cut surface was grayish pink, dotted with minute yellowish-white areas.

The right kidney weighed 200 Gm., the left 240 Gm. The surface of both kidneys was not only covered with numerous petechial hemorrhages, but showed sharply localized grayish-yellow and opaque areas, which protruded above the surface of the organ, and which also extended to a depth of about 1 cm. into the renal substance. On cut surface both kidneys were pale, and mottled with many areas of opaque yellowish white. The capsule was very thin and stripped off with great difficulty; the glomeruli could not be distinguished, and the pyramids were indistinctly demarcated. The pelves contained petechial hemorrhages.

The heart weighed 275 Gm., and except for petechial hemorrhages which covered the epicardium, appeared normal.

The right lung weighed 540 Gm.; its lower lobe was reddish, mottled with deep reddish black. The left weighed 350 Gm. and seemed to be normal.

The liver weighed 1,910 Gm., and appeared somewhat grayish and softer than usual. The gallbladder was normal.

The bone-marrow from the femur appeared as a grayish-yellow fluid mass. The bone trabeculae seemed to be slightly atrophic.

On removal of the normal appearing meninges, the cerebral convolutions were found to be considerably flattened. Two areas of softening about 2 cm. in diameter were seen in the anterior portion of the frontal lobe, one area on the under surface of the right parietal lobe and two in the occipital region. On cut surface numerous lymphomas varying in size from 1 mm. to 2 cm. were found scattered throughout the hemispheres (fig. 1).

Microscopic Examination.—The heart was moderately infiltrated with lymphoid cells which lay between the cardiac striations. In the epicardium small lymphomas were present. The organ showed slight edema and dilatation of the vessels, which

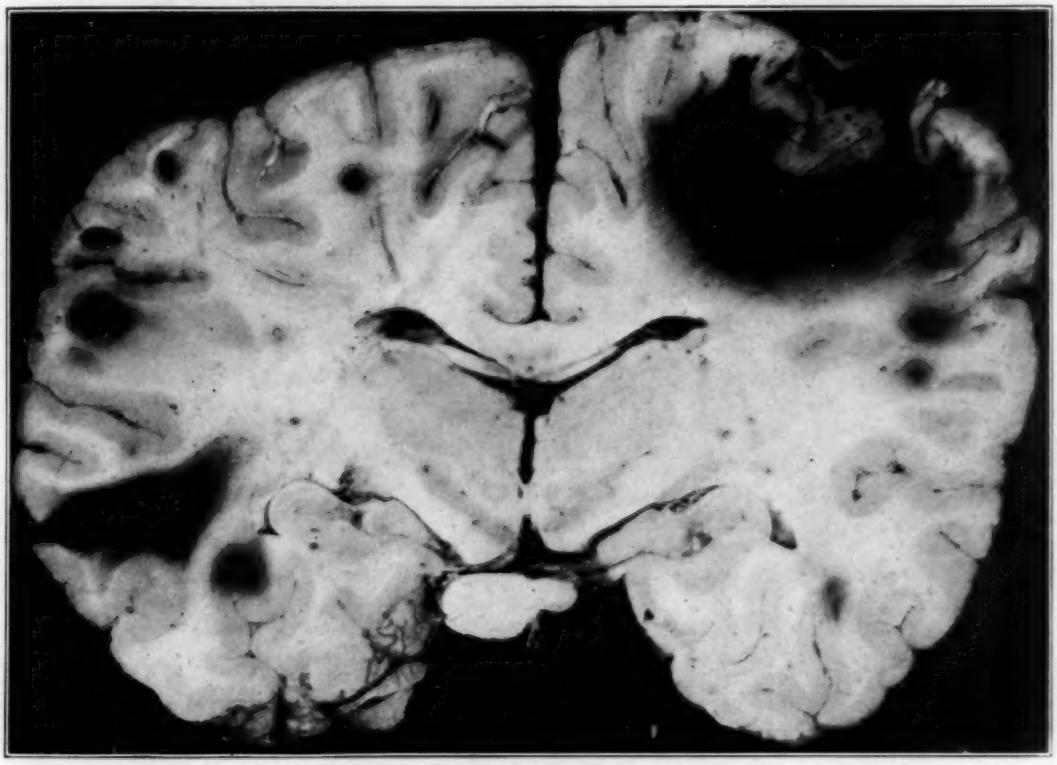

Fig. 1.—Leukemic lymphadenosis showing hemorrhages and lymphomas on section through the postcentral region. All other parts of the cerebrum were similarly involved.

were, however, practically bloodless, but contained a moderate amount of lymphoid cells. The vascular endothelium was swollen. The cardiac muscles showed fragmentation and fatty infiltration.

The vessels of the lungs were widely dilated and densely packed with lymphoid cells with an insignificant admixture of red cells. Lymphoid cells were also seen heavily infiltrating the alveolar capillaries. In places the alveolar walls were ruptured by wide hemorrhages, and in others they were dilated. No signs of inflammation were seen in the organ.

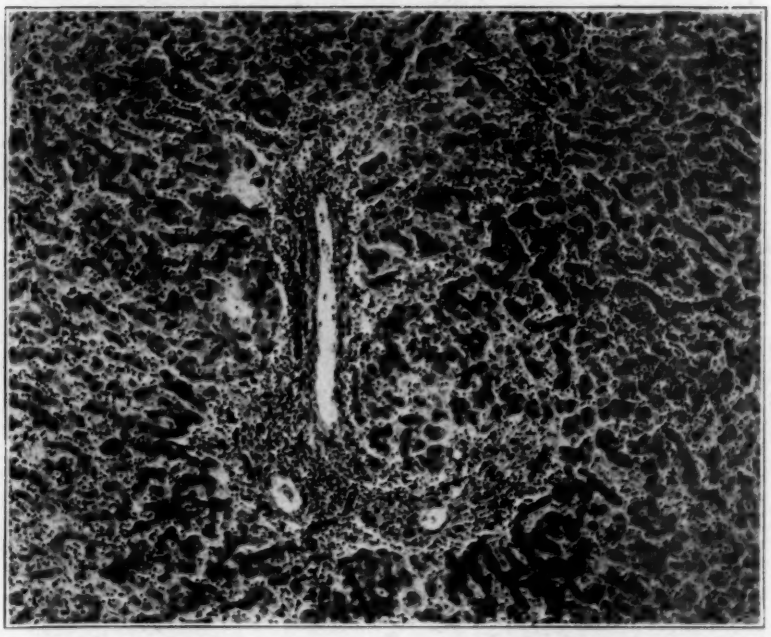

Fig. 2.—Leukemic lymphadenosis. Liver, showing a circumscribed infiltration by lymphoid cells (lymphoma) of the portal area. Methylene blue-eosin; × 80.

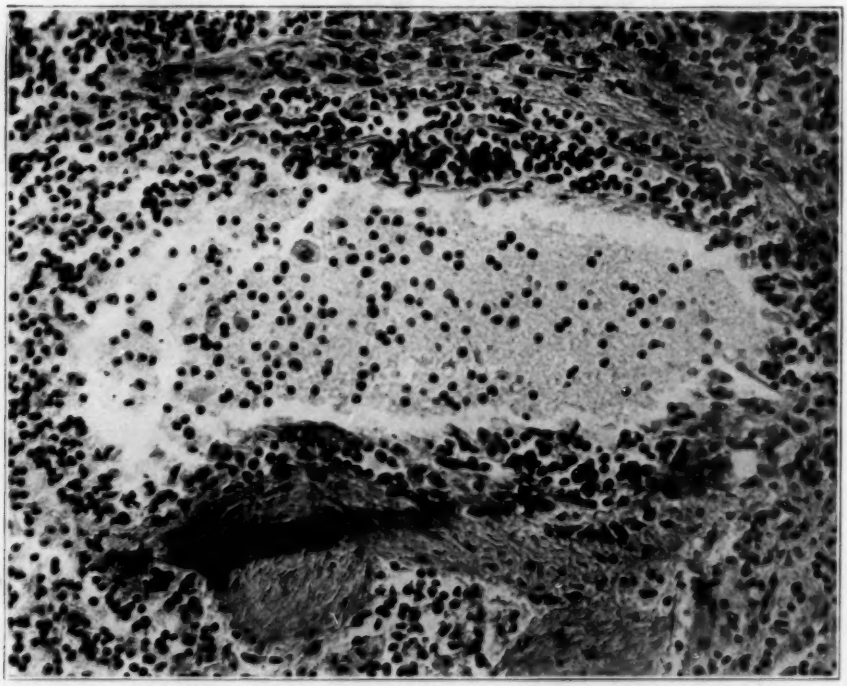

Fig. 3.—Leukemic lymphadenosis. Spleen, showing invasion by lymphoid cells of the vessel wall leading to dissociation of its fibers. Methylene blue-eosin; × 250.

The periportal areas of the liver contained only lymphomas[3] (fig. 2). The hepatic capillaries contained lymphoid cells which were scant, being arranged in single files. There was an abundance of fat in the organ.

The lymphoid cells of the kidneys were scattered between the tubules, leading in a few areas to their compression. The infiltration seemed to be heavier around the glomeruli. The latter contained only a few lymphoid elements, but were enlarged and generally bloodless. With Herxheimer's stain the endothelium of the capillaries showed the presence of fat. Bowman's capsule was unaltered. The vessels were dilated, and their walls contained here and there lymphoid cells.

The germinal centers of the spleen were mostly obliterated. Small lymphoid cells were uniformly distributed over the sections, mingled with red blood cells. Large cells with eosinophilic granules were seen occasionally. Mitoses were not frequent.[4] A prominent feature in the sections is a heavy invasion by lymphoid cells of the wall of the blood vessels (fig. 3), leading to a distortion of fibers with obliteration of the vascular structure. The sections contain numerous plasma cells.[5]

The thymus, which was uniformly infiltrated with small lymphoid cells and with plasma cells, could be identified only by the presence of a few Hassal corpuscles. As in the spleen, the walls of the blood vessels were also invaded by lymphoid elements.

In the lymph nodes lymphoid cells invaded the capsule, forming small lymphomas.

In the cerebral cortex lymphoid cells abounded in the larger vessels and capillaries, which they literally occluded. In only a few instances cells seemed to lie freely in the perivascular spaces of His or in the cerebral parenchyma.

Beneath the cortex there were numerous lymphomas. They varied greatly in size, and were made up of lymphoid elements without any admixture of blood

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3. Naegeli (Blutkrankheiten und Blutdiagn, 1923), affirms that circumscribed periportal infiltration is characteristic of leukemic lymphadenosis, while a diffuse intracapillary infiltration occurs only in leukemic myelo-adenosis. This, according to Naegeli, once more militates for the "dualistic" theory of the genesis of leukemia.

4. Ellermann (Messung der Mitosenwinkel als methode zur Unterscheiden Verscheidener "lymphoider" zellformen, Folia Haemat [Archiv.] **28**:207, 1923; **30** February, 1924) has recently called attention to some particularities of the mitotic figures in leukemia. According to his investigations, the size of the apical angle (Spitzenwinkel) in leukemic lymphadenosis is approximately 40 degrees, while in leukemic myelo-adenosis it measures about 66 degrees. This is of importance in the differential diagnosis between the two varieties of leukemia, which in acute cases presents great difficulties.

5. The presence of plasma cells in cases of leukemic lymphadenosis is frequently a prominent feature in one or several glands. Occasionally it involves the entire body. Ghon and Roman (Über Psdudo-leukämische und Leukäm. Plasmazellen hyperplasie, Folia Haemat. [Archiv.] **15**:73, 1913) consider such cases as a separate group of leukemia, which they define as "leukemia plasmacellulare" and which, according to these authors, may be leukemic and aleukemic. Some writers regard this process of the blood as a hyperplasia, and the tumors composed of plasma cells as plasmocytoma. Schridde (Aschoff: Pathologische Anatomie **2**:120, 1923) says that this peculiar type of tumor (plasmacytoma) behaves somewhat like a myeloma. Sternberg affirms that the presence of plasma cells in these tumors is due to inflammation which is always present in leukemia.

(fig. 4). They were sharply demarcated from the cerebral parenchyma (figs. 4 and 5). In one section there was (fig. 6) a hemorrhage containing numerous lymphoid cells, in the center of which lay a blood vessel whose walls showed traces of distorted fibers. The smaller and larger vessels in such hemorrhagic areas were all widely distended by masses of lymphoid cells which were also present in the perivascular spaces. The walls of these vessels showed changes of the intima and media, which were no longer distinguishable.

A single small lymphoma was also found in the cerebellum. Minute lymphomatous nodules but no hemorrhages were present in the medulla oblongata. The leptomeninges contained no lymphoid cells; they were found in the perivascular spaces only.

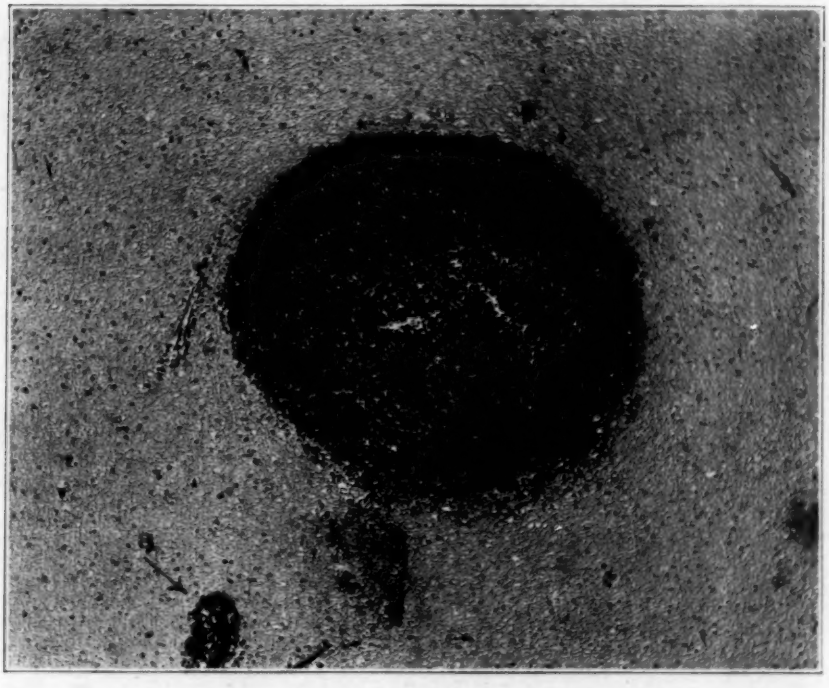

Fig. 4.—Leukemic lymphadenosis, showing a small lymphoma in the brain. *a*, "thrombosis" of a capillary by lymphoid cells, which crowd also the pericapillary space. Methylene blue-eosin; × 80.

The cerebral parenchyma as a whole showed marked edema (fig. 5). The entire structure had a spongy, honeycombed appearance particularly noticeable in the vicinity of the lymphomas.

Near the large hemorrhages and lymphomas the ganglion cells were shrunken or sclerosed. With Bielschowsky's stain they were small and homogeneous, and their axon cylinders as well as dendrites were short, thick, sinuous and vacuolated. In the parts remote from hemorrhages, the cytoplasm of the cells showed tigrolisis and a diffuse vacuolization, due to a deposit of lipoids, as revealed with Herxheimer's stain. The nuclei were often vaguely outlined and also vacuolated.

In the nerve fibers the myelin sheaths were only occasionally lacking, but as a rule they invested the axon cylinder showing irregularities in outline and fenestra-

tion (fig. 7). The axons themselves showed pronounced lesions—neurolytic swelling, thickening and vacuolization (fig. 8) only near the hemorrhage; otherwise they were slightly swollen and were less affected as compared with the myelin sheaths.

There was practically no gliosis in the sections. The glia cells showed changes of a progressive character—hyperchromatic nuclei, fatty infiltration. There was an abundance of rod cells (Stäbchenzellen) which could be seen almost in every field in the cortex. Gitter cells (Gitterzellen[6]) were seen in a few instances in the cortical layer.

There is a proliferation of adventitial cells and progressive changes in the endothelium: hyperchromatosis and swelling.

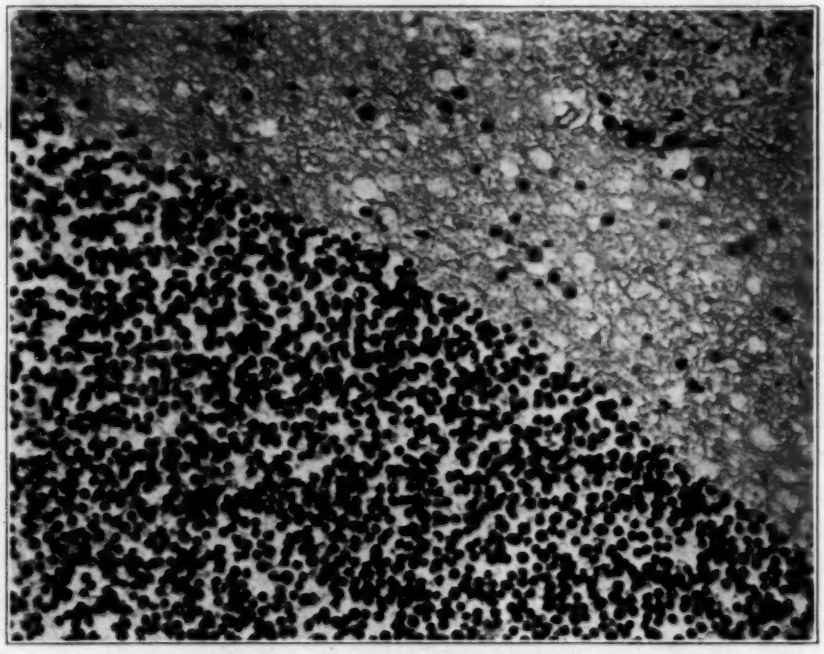

Fig. 5.—Leukemic lymphadenosis. A large lymphoma of the hemispheres. The cerebral parenchyma shows marked edema. Methylene blue-eosin; × 300.

6. The interstitial cells of the brain were considered up to the last few years as being composed of two varieties of astrocytes—protoplasmic and fibrillary and the so-called "adendritic corpuscles" or "third element" of Cajal. By the use of special stains Rio del-Hortega has shown that: (1) the "adendritic corpuscles" are in reality provided with very complicated processes, (2) they are two different varieties of cells, designated by him as "oligodendroglia," which analogous to astrocytes are of ectodermal origin, and "microglia," which are of mesodermal origin. The "microglia" are believed to play an outstanding rôle in various pathologic processes of the brain. The "Stäbchenzellen" and "Gitterzellen," according to investigations, are nothing other than transformed microglia which in their new phagocytic rôle have taken on new aspects.

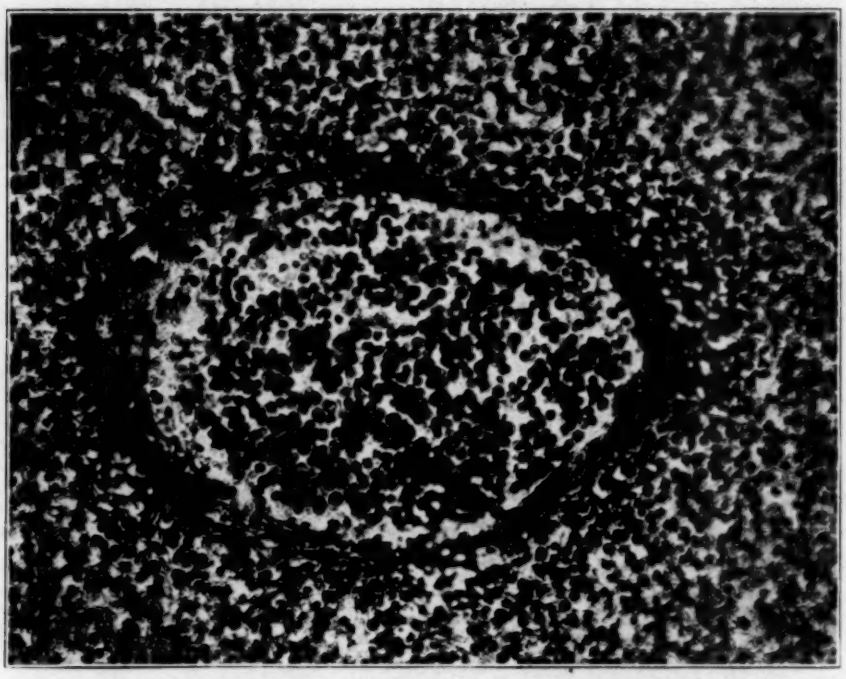

Fig. 6.—Leukemic lymphadenosis. A greatly dilated and ruptured cerebral vessel. The lymphoid cells are mingled with red blood cells. Methylene blue-eosin; × 300.

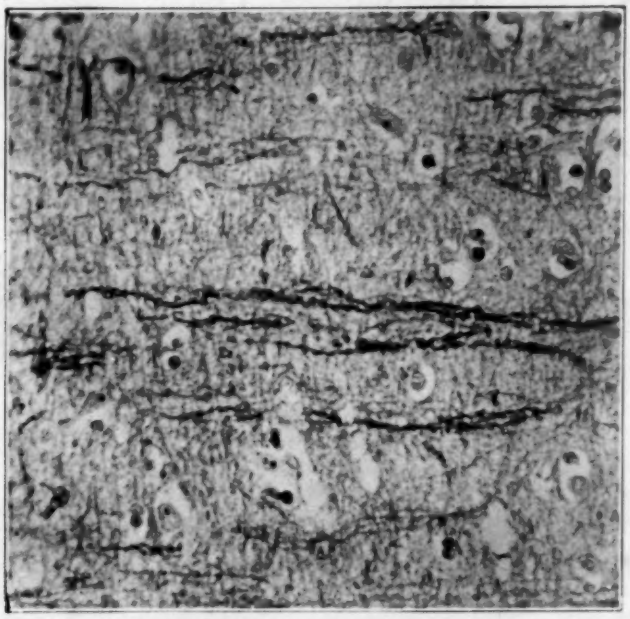

Fig. 7.—Leukemic lymphadenosis, showing swelling and fenestration of the myelin sheaths. Loyez' stain for myelin sheaths; × 300.

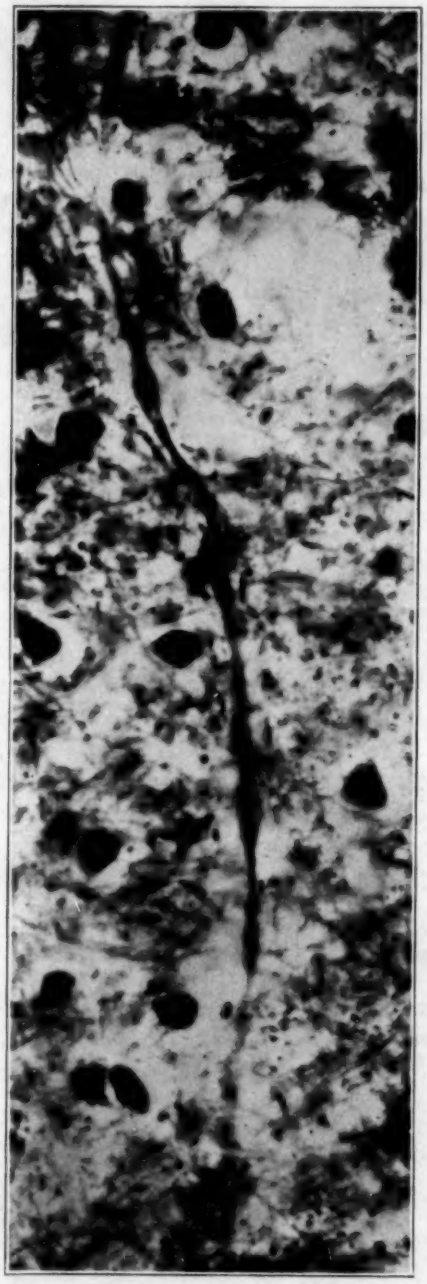

Fig. 8.—Leukemic lymphadenosis, showing marked regressive changes in the axis cylinder. Bielschowsky's stain; × 850.

Summary.—A case of leukemic lymphadenosis has been described in which in addition to the characteristic and well-known changes occurring in the viscera, lymphomas and hemorrhages were found to be widespread in the brain.

COMMENT

The pathogenesis of hemorrhages in leukemia, which are apparently of frequent occurrence, lies primarily in the damage of the vascular coats. The lymphoid cells are aggressive toward the vessel wall, frequently invading it, dissociating its fibers, and leading to the formation of lymphomas (fig. 3).

A second factor which favors these extravasations is the capillary stasis and "thrombosis" of smaller and larger vessels due to the increased amount of white cells in the blood. The damaged capillaries, as shown by some writers, often form outpocketings (miliary aneurysms?) which rupture and lead to the formation of petechiae, ecchymoses, etc.

"Thrombosis" of the vessels of the corpora cavernosa penis is also considered to be the cause of the priapism known to be a not infrequent complication.[7]

The formation of lymphomas in tissues like the brain, where the lymphoid cells are normally absent, is obviously due to the passage through the vascular wall of lymphoid cells which invade the surrounding tissue and occasionally form large lymphomatous nodules which subsequently grow as autochthonous units. This phenomenon is defined as colonization (by emigrating blood elements), and is therefore a process quite different from that whereby metastases of malignancy are implanted.

The histologic changes found in this case in the cerebral elements themselves, though grave in character, cannot be considered as being specific for leukemia. The degeneration found in the glial and nervous elements—fatty infiltration, swelling and fenestration of the myelin sheaths, etc.—was diffusely scattered all over the organ without any particular predilection for the perivascular spaces, as is observed for instance in primary anemia. Similar changes of a various intensity are often seen in primary and metastatic malignancy of the brain—carcinoma and sarcoma—and are due apparently to mechanical and toxic influences.

CASES FROM THE LITERATURE

Involvement of the Meninges and Hemispheres by Hemorrhages or Lymphomas.—The following thirteen isolated examples have been found:

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7. Widal, F.: Hématome et priapisme dans la leucémie myéloide, Bull. et mém. Soc. méd. d. hôp. de Paris **17**:816 (June 22) 1900. Moure, P., and Leibovici, R.: Le priapisme leucémique, J. d'Urol. **19**:101 (Feb.) 1925.

1. Friedländer, C.:[8] A man, aged 30, complained of headaches and deafness at first of one ear and later of both. About six weeks before death, he had begun to lose vision. Examination showed a large spleen. He died of apoplexy. Necropsy showed multiple leukemic nodules in the brain and retina and also fresh hemorrhages in the left corpus striatum.

2. Bramwell:[9] The patient complained of severe headaches and had become maniacal. At necropsy numerous small hemorrhages were found in the white substance. The vessels and perivascular spaces were filled with tumor cells.

3. Ebstein:[10] A man, aged 23, ill for about four weeks, complained of headaches and loss of appetite. At necropsy the pia mater cerebri and both trigeminal nerves contained multiple hemorrhages. In the sheath of the right facial nerve was found "brown pigment" (apparently blood). Throughout the white substance of the brain and also in the cerebral nuclei were disclosed minute bleedings.

4. Westphal:[11] A young man, aged 16, was admitted to the clinic complaining of bleeding from the nose and mouth. His body was covered with petechiae; he was weak, anemic and complained also of vertigo and headaches. Necropsy showed a recent hemorrhage in the inner surface of the dura; a few small hemorrhages were also found in the brain substance.

5. Guttmann:[12] A boy, aged 10, was admitted to the clinic complaining of bleeding from the nose and mouth. Examination showed numerous petechiae and ecchymoses and priapism. The necropsy showed a large amount of blood in the left lateral ventricle, whence it reached the corpus striatum and the thalamus opticus; a hemorrhage about 2 cm. in diameter was found in the right parietal lobe.

6. Strauss:[13] A child, aged 13 months, ill with leukemic lymphadenosis accompanied by cutaneous, serous and mucous petechiae, a few days before death was delirious. Necropsy showed numerous hemorrhages beneath the skull cap, underneath the dura and in the pia. The brain was not unusual on macroscopic examination.

7. Kwasniewski:[14] A woman, aged 47, exhibited petechiae over the body, with bleeding from the nose, mouth and genitalia. Necropsy showed a wide subdural hemorrhage in the left hemisphere.

8. Benda:[15] Second case. The patient died of apoplexy. Necropsy showed a red softening of the right hemisphere, small bleedings and a lymphoma in the pons. The nerve substance was infiltrated with lymphoid elements in only a few instances without producing changes in the nerve cells or nerve fibers.

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8. Friedländer, C.: Pathologisch-Anatomische Mitteilungen Ein Fall von multiplen leukemischen Neubildungen des Gehirns und der Retina, mit dem Klinischen Ercheinungen eines Hirntumors, Virchows Arch. f. path. Anat. **78**:362, 1879.

9. Bramwell, B.: A Remarkable Lesion of the Nerve Centers in Leucocythemia, Brit. M. J., June 12, 1886, p. 1098.

10. Ebstein, W.: Ueber die akute Leukämia und Pseudoleukämia, Deutsches Arch. f. klin. Med. **44**:343, 1889.

11. Westphal: Ueber ein Fall von Akuter Leukämie, München. med. Wchnschr. **37**:4, 1890.

12. Guttmann, P. L.: Ueber einen Fall von Leukemia Acutissima, Berl. klin. Wchnschr. **28**:1109, 1891.

13. Straus, H.: Ein Fall von Akuter Leukämie, Arch. f. Kinderh. **30**:272, 1900.

14. Kwasniewski: Ein Beitrag zur Klinik und Histogenese der akuten myeloblastichen Leukämie, Deutsches Arch. f. klin. med. **83**:145, 1924.

15. Benda, C. L.: Leukämische Erkrankungen des Central Nervensystems, Berl. klin. Wchnschr. **35**:228, 1898.

9. Benda:[15] First case. Lymphomas were found in the dura and also a hematoma which led to compression of the brain.

10. Spitz:[16] At necropsy multiple lymphoid foci mostly confined to the white substance were scattered over the brain. Changes were found in the myelin sheaths. The axis cylinders were frequently naked.

11. Lauenstein:[17] A poorly nourished man, aged 59, with a general glandular enlargement and numerous subcutaneous tumorous nodules died from apoplexy. Necropsy showed most of the left occipital lobe to be destroyed by a hemorrhagic focus. The surrounding cerebral substance contained numerous small hemorrhagic areas.

12. Kretschy:[18] The patient was admitted to the hospital with complete left-sided hemiplegia which came on without loss of consciousness. At necropsy one large vessel was found to be obstructed by tumor cells. Numerous small hemorrhages were present throughout the brain.

13. Fränkel:[19] A man, aged 18, complained of weakness and bleeding from the nose. While in the hospital he developed a hemiplegia. At necropsy minute hemorrhages were found in the hemispheres.

Bleeding in the central nervous system in leukemia, to judge from these accounts, is therefore less uncommon than generally supposed. In the thirteen cases hemorrhages in the brain led in three instances (nos. 11, 12 and 13) to hemiplegia. The low figures for cerebral lesion of this sort in leukemic lympho-adenosis and myelo-adenosis which are generally given are probably explained as follows. In the first place, minute cerebral hemorrhages may give no distinctive clinical signs, and large hemorrhages usually occur a short time before death; the clinician is little concerned with this terminal affair. This was true, for example, in the case of the primary subject of this report. Then, too, in most pathologic laboratories necropsies are usually limited to an examination of the body, and in consequence lesions of the nervous system are often overlooked.

The pathogenesis of bleeding in its association with the formation of lymphomas in the central nervous system has been discussed in connection with the personal observation.

Involvement of the Cranial Nerves.—Seven examples have been found. In two the acoustic nerve was involved, in five one or both facial nerves.

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16. Spitz, R.: Zur Kenntniss der Leukämischen Erkrankungen des Central Nervensystems, Deutsche Ztschr. f. Nervenh. **19**:467, 1901.

17. Lauenstein, C.: Zur Pathologie der Leukämie, Deutsches Arch. f. klin. Med. **18**:120, 1876.

18. Kretschy, F.: Ein Fall von Leukämie mit ausgebreiteten Hemorrhagen, Wien. med. Presse **19**:137, 1878.

19. Fränkel, A.: Ueber ein Fall von Leukämia Lymphatica, Ztschr. f. klin. Med. **3**:405, 1881.

14. Alt and Pineles:[20] A man, aged 66, with a negative past history complained of sudden ringing in the ears, soon followed by deafness and severe vertigo. One month later, he developed pain and swelling of the shoulder, which brought him to the clinic. He died four months after the inaugural symptoms. The necropsy showed the lateral, medial and intramedullary parts of the acoustic nerve to be infiltrated with leukemic elements. In areas the nerve roots appeared to be enveloped in leukemic cells. The pia was thickened and also infiltrated with cells. The nerve fibers were atrophic.

15. Rydberg:[21] In this case there was a disturbance of both labyrinths. In one ear it came suddenly, in the other the onset was gradual. The necropsy showed a cellular infiltration around the acoustic nerve and the labyrinth.

The lesion of the acoustic nerve in both of these cases was apparently mechanical in origin due to compression of the nerves by the infiltrated lymphoid cells. In case 14 there was also an infiltration of the pia mater.

16. May:[22] In a typical case of a chronic leukemic lymphadenosis, a right-sided facial paralysis occurred. Necropsy revealed a circumscribed leukemic infiltration of the right seventh nerve, with degeneration of the nervous substance and fatty infiltration.

Similar to cases 14 and 15, the involvement of the cranial nerve in this case was also mechanical in origin due to a perineural infiltration by lymphoid cells leading to its degeneration.

17. Eisenlohr:[23] A man, aged 19, with a typical history of a leukemic lymphadenosis, developed a bilateral facial paralysis, with temporary evidence of involvement of the second and third branches of the trigeminus, as well as some disturbances of the hypoglossus and glossopharyngeus. At necropsy a collection of blood was found in the subdural space of the frontal lobe. There were hemorrhages in the neurilemma of the left seventh, tenth and twelfth, and in the right tenth, eleventh and twelfth nerves. On microscopic examination, these nerves were found to be infiltrated with lymphoid cells. There were also multiple hemorrhages. Both seventh nerves showed degeneration of the sheaths and fibers.

18. Müller:[24] Clinically there was a bilateral facial paralysis, a lingual palsy, abolition of reflexes of the soft palate and upper part of the posterior pharyngeal wall, difficulty in deglutition and sensory disturbances in the trigeminus, with absence of corneal reflexes. Necropsy showed multiple hemorrhages in the neurilemma and substance of both facial, left lingual and inferior alveolar, right vagus and accessory nerves. The nerves were also infiltrated with lymphoid elements. There were also cord lesions (see case 26).

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20. Alt and Pineles, F. L.: Ein Fall von Morbus Ménière, bedingt durch leukämische Erkrankung des nervus acusticus, Wien. klin. Wchnschr. **9**:849, 1896.

21. Rydberg: Ein Fall von myelogenes Leukämie mit Zerstörung des Labyrinths, Hygiea **78**:898, 1916.

22. May: Eine Seltene Ursache peripheralen Facialslähmung, quoted by Bloch and Hirschfeld (cf footnote 34).

23. Eisenlohr, E. L.: Neuropathologische Beobachtungen, Virchows Arch. f. path. Anat. **73**:56, 1878.

24. Müller, W.: Ueber Veränderung des Nervensystems bei Leukämie, Inaug. Dissert., Berlin, 1895.

19. Kast:[25] The patient, aged 50, showed on admission a marked degree of deafness and tinnitus of recent origin, paresis of all branches of the right facial nerve and a very sluggish reaction of the pupils to light and accommodation. Two weeks after admission, the left facial nerve showed changes similar to those of the right. There were no bulbar symptoms. The reflexes were normal. On histologic examination changes were found in the nuclear region of the hypoglossus, glossopharyngeus, vagus, acusticus and facialis. The ganglion cells were decreased in number, were granular and occasionally contained pigment. There was no gliosis or changes of the vessels. Numerous nerve fibers were atrophic, and the cerebral substance showed areas of degeneration.

20. Hellgardt:[26] A man, aged 30, with a leukemic lymphadenosis which ran a subacute course, was admitted to the clinic complaining of a complete bilateral facial paralysis. He did not long survive. A subsequent examination showed that both facial nerves were heavily infiltrated with lymphoid cells.

Bilateral paralysis of the facial nerves (diplegia facialis) is a rare lesion, occurring in basilar syphilitic meningitis and occasionally in fracture of the skull. In the four cases recorded above, it was due to bilateral hemorrhages and lymphoid infiltration leading to degeneration of the myelin sheaths and the axis cylinders.

It will be noted that in some of these cases, not only the facial and acoustic nerves were involved in the leukemic process, but to a less extent other cranial nerves as well.

Involvement of the Spinal Cord.—This was shown in eleven cases, in one of which an involvement of the cranial nerves was also observed (Cf case 18).

21. Eichhorst:[27] The patient, aged 17, had complete motor paralysis of both legs. There was focal paresthesia and difficulty in urination, but no sensory disturbances. One month before death he showed a hyperesthesia up to the level of the chest, incontinence of feces and urine and sluggish patellar reflexes. At necropsy the posterior part of the spinal cord between the fifth and seventh thoracic vertebra was obliterated by a lymphoma which was adherent to the dura and bone. The cord was compressed and soft in this area. Microscopically, the white substance of the anterior and lateral tracts showed a spongy, cellular mass containing swollen naked axis cylinders; the posterior horn showed a slight sclerosis. Above and below the compression a secondary degeneration was found in Gall's and Gowers' tracts.

22. Baudoin and Paturier:[28] A man, aged 64, after three months of pain in the lumbar region felt a sudden and violent pain in the lower extremities, followed by an almost immediate paralysis of both legs. He died three days after this attack. Histologically, the spinal cord showed two lesions: (1) a subacute myelitis (lesions of the motor horn cells, swelling of the cylinder axis and hyaline degeneration of the vessels), more marked in the upper dorsal region; (2) an area of softening at the level of the fifth dorsal segment.

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25. Kast: Beitrag zur Pathologie der Leukämie, Ztschr. f. klin. Med. **28**:79, 1895.

26. Hellgardt, H.: Diplegia Facialis bei Leukämie, Inaug. Dissert., Königsberg, 1917.

27. Eichhorst: Ueber Erkrankungen des Nervensystems in Verlaufe der Leukämie, Deutsche Arch. f. klin. Med. **61**:519, 1898.

28. Baudoin, A. L., and Paturier, G.: Sur les complications nerveuses des leucémies, Rev. neurol. **18**:673, 1910.

23. Stursberg:[29] A man, aged 30, complained of severe pain of sudden onset in the back, which radiated to the legs. In the next twenty-four hours there was a total paralysis of the legs with loss of sensation and abolition of knee and ankle reflexes. He died eleven days later. A postmortem examination showed the dura of the lower thoracic and lumbar cord to be surrounded by a reddish-brown mass 1 cm. thick, in which the roots were embedded. On histologic examination the epidural mass was composed of myeloid cells. The cord showed ascending degeneration.

24. Bassoe:[30] A woman, aged 38, had a history of leukemia for about three years. About five weeks before death, she developed paralysis of the legs. Necropsy showed the dura at the level of the fourth, fifth and sixth thoracic vertebra to be covered by a firmly adherent layer of grayish tissue for a distance of 12 cm. On the left side, both anterior and posterior roots passed through it. The entire cord was surrounded for a distance of 2 cm., the right and posterior surface escaping elsewhere. The inner surface of the dura was smooth, and the pia appeared normal. On cut surface the thickened dura in the thoracic region of the cord appeared almost necrotic in its posterior half, and the normal markings were lost in most cut surfaces. At the level of greatest dural thickening the cord was flattened laterally. Histologically, the spinal cord in the region compressed by the epidural mass showed marked degeneration and partial necrosis in its portions. The rest of the cord showed only moderate secondary degeneration.

25. Dolivo:[31] A man, aged 50, developed leukemia following sepsis. About four months before death, he developed a paraplegia followed in a few days by sensory disturbances. The necropsy showed softening of the cord in the area of the tenth dorsal vertebra and downward, which involved principally the column of Clarke. There was a hemorrhage, a lymphocytic infiltration and vascular changes in the area of the twelfth dorsal. The lateral cerebellar peduncles and Gowers' tract were also degenerated.

26. Müller, W.:[24] (Cf. case 18). The cord showed degeneration of Gall's and partly of Burdach's tracts. In the latter, degenerated fibers and lacunae were found singly and in patches. These foci showed destruction of fibers, thickening and gliosis.

27. Nonne:[32] (First case). The anterior, lateral and posterior pyramidal tracts contained asymmetrical foci of invasion by myelocytic elements, which were present in the cervical, middle dorsal and partly in the lumbar regions. In some of the foci the myelin sheaths and axis cylinders showed swelling. In a few instances the myelin sheath was lacking entirely, and the axis cylinder represented débris. There were no hemorrhages or round cell infiltration, nor were changes found in the vessels. A slight sclerosis was present in the cervical part, and a symmetrical degeneration in the lateral part of Gall's and Burdach's tracts.

28. Nonne: (Second case). Microscopically the spinal cord showed small foci of degeneration in the white substance in the anterior tract.

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29. Stursberg, H.: Zur Kenntnis der nervösen Erkrankungen bei Leukämie, Deutsche Arch. f. klin. Med. **114**:292, 1914.

30. Bassoe, P.: Leukemic Infiltration in the Spinal Canal as a Cause of Paraplegia, J. Nerv. & Ment. Dis. **47**:180, 1918.

31. Dolivo, V. H.: Ein Fall von Leukämie mit Veränderungen am Zentralnervensystem, Inaug. Dissert., Heidelberg, 1919.

32. Nonne: Ueber degenerations Herde in der weissen Substanz des Rückenmarks bei Leukämie, Deutsche Ztschr. f. Nervenh. **10**:105, 1897.

29. Schulze, H.:[33] Lesions were found in the dorsal and cervical parts of the cord, confined to all tracts, and consisting in swelling and destruction of the axis cylinders.

30. Bloch and Hirschfeld:[34] A girl, aged 8 months, with a blood picture typical of leukemic lymphadenosis, was admitted in a somnolent state. Necropsy showed no macroscopic changes in the central nervous system, but on microscopic examination a diffuse sclerosis of the brain and spinal cord was disclosed. The cord was also infiltrated with lymphoid cells.

31. Gardiner and Lartigau:[35] The spinal cord showed definite degeneration of that part of the posterior internal columns bordering the posteromedian septum. This degeneration was traceable from the end lumbar to the lower cervical region where it ceased to exist. The peripheral nerves were normal.

In three of the cases reviewed above (cases 20, 22 and 23), the cord lesion was obviously due to pressure on this structure by lymphomas which had primarily infiltrated the meninges; in the other eight instances, the process appears to have been degenerative in character (myelosis), similar, according to Nonne,[36] to the cord lesions seen in primary anemia. The same author found cachexia and spinal cord lesions in cases of chronic alcoholism with anemia of the pernicious type. It has been reported to occur also in lead poisoning, in scurvy and beri-beri.

The pathology of the spinal lesion in pernicious anemia has recently been the object of special attention by a number of investigators. It has been pointed out that the process for some unknown reason is usually localized in the posterior and lateral columns of the lower cervical and upper thoracic segments of the cord. The microscopic details of the lesions are typical in that they begin around and spread from the vessels, which serves as an argument for the hematogenous transmission of the hypothetical "toxin." They consequently have a focal "spotty" character.

The exact nature of the lesion is as yet undetermined. According to Henneberg,[37] it consists essentially of a primary degeneration of the nerve fibers which begins with a swelling and decay of the myelin sheaths. The process of destruction of the axis cylinders is much

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33. Schulze, H.: Ueber des vorkommen gequollener Axencylinder in Rückenmark, quoted by Spitz (footnote 16).

34. Bloch, E., and Hirschfeld, H.: Zur Kenntniss der Veränderungen am Centralnervensystem bei der Leukämie, Deutsche Ztschr. f. klin. Med. **37**:32, 1900.

35. Gardiner, H., and Lartigau, A.: A Case of Lymphoid Leukemia Showing Degeneration of the Postero-internal Column of the Spinal Cord, Albany M. Ann., July 23, 1902, p. 339.

36. Nonne: Ueber Myelitis intrafunicularis und über combinierte Strängerkrankungen bei Alkohol, Monatschr. f. Psychiat. **20**:497, 1906.

37. Henneberg, R.: Atypische Formen der Funiculären Myelitis, Klin. Wchnschr. **3**:920, 1924.

slower, and normal axons can often be found within swollen myelin sheaths. He finds no changes in the gray substance. The studies of Schimazono,[38] Wholwill[39] and Weimann,[3] on the other hand, have a different conception of the process. The lesion in the experience of these writers is primarily confined to the axis cylinders (neurolytische Schwellung), followed soon by degenerative changes in the myelin sheaths. The opinion of these authors is of interest in that the myelin sheaths are considered to be as a rule the locus minoris resistentiae of the nerve fiber, being, usually, primarily affected by noxious agents of any kind (Spielmeyer[40]). It appears, then, that the hypothetical "toxin" of pernicious anemia has a particular affinity for the axis cylinder, while the myelin sheaths are only secondarily affected.

It will be seen from the foregoing that there is no unanimity as to the microscopic details of the lesion in primary anemia; hence, Nonne's assertion to the effect that the lesions of the central nervous system in leukemia and pernicious anemia are similar cannot be fully relied on. It cannot be denied, however, that there are analogies between the two affections, as evidenced by the few abstracted and herein reported cases.

SUMMARY AND CONCLUSIONS

A case of leukemic lymphadenosis is reported, and thirty cases of leukemic lymphadenosis and myelo-adenosis from the literature, involving the central nervous system, are reviewed.

In the author's case a patient with a subacute leukemic lymphadenosis died of apoplexy, and at necropsy numerous lymphomas and hemorrhages were found in the brain. Grave degenerative changes were found in the interstitial, parenchymatous and mesenchymal elements of the brain, more pronounced in the vicinity of the extravasated blood and also around the lymphomas. These changes are not regarded as peculiar to leukemia, but are ascribed to circulatory disturbances in the brain due to hemorrhages and accumulated masses of lymphoid elements (similar lesions of a minor degree occur in primary and secondary malignancy of the brain).

In the thirty cases gathered from the literature, lesions of the nervous system have been reported in the hemispheres in twelve, in the cranial nerves in eight and in the cord in eleven cases, in eight of which spinal

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38. Schimazono: Ueber das Verhalten des Zentralen und Peripherischen Nervensystem bei verscheidenen Vergiftungen und Ernährungstörungen, Arch. f. Psychiat. **53**:972, 1913-1914.

39. Wholwill: Zum Kapitel der pathologisch-anatomischen Veränderungen des Gehirns und Rückenmarks bei Perniziösen Anämie, Deutsche Ztschr. f. Nervenh. **68-69**:488, 1921.

40. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Julius Springer **1**:111, 1922.

degenerations were observed in the absence of lymphomas, in many respects resembling those observed in pernicious anemia.

Hemorrhages in leukemia are primarily due to vascular lesions produced by (1) stasis in the capillaries and "thrombosis" of the vessels by lymphoid cells, (2) the invasion of the vessel walls by the lymphoid cells with dissociation of the vascular coat and (3) the hypothetic "toxin" which circulates in leukemic blood.

The occurrence of lymphomas in organs or structures in which lymphoid tissue is normally absent (as in the brain) is due to the passage of the vascular wall by lymphoid cells, with the ultimate formation of large nodules which occasionally grow as autochthonous units. This phenomenon is defined as "colonization" by lymphoid elements and is to be distinguished from metastases in malignancy.

HEALED DISSECTING ANEURYSM OF THE AORTA

REPORT OF A CASE WITH PATENT DUCTUS ARTERIOSUS AND ENORMOUS HYPERTROPHY OF THE HEART *

ERNEST M. HALL, M.D.
SAN FRANCISCO

Although it is generally conceded that Laennec, 1826, was the first to describe dissecting aneurysm, Broca gives Maunoir the credit for first using the term and describing the condition in a work published in 1802 (Peacock [1]). During the century since Laennec's publication there have been reported in the literature, according to Moosberger,[2] 274 cases. He states that out of this number it had been possible to make the clinical diagnosis in only three cases. According to the statistics of Frei as quoted by Moosberger, the aorta is affected in by far the greater number of cases. In 239 of the 273 cases (87.5 per cent) the disease was located in the aorta. The part of the aorta most frequently affected, according to the same authority, is the portion directly above the aortic valve. In 153 of the 239 cases (64 per cent) of those occurring in the aorta, this was the site of the primary lesion. As to the location of the separation in the coats of the vessel wall, statistics show that the tear in most instances occurs in the outer portion of the media, but may also occur between intima and media.

Peacock, in 1863, collected from the literature eighty cases of dissecting aneurysm. From a study of these cases he concluded that two factors were responsible for the condition: (1) the inner coat of the vessel was "unduly lacerable," and (2) the heart beat with increased power or undue violence.

In 1887, Boström [3] described eighteen cases of healed dissecting aneurysm. It was his opinion that trauma is chiefly responsible for this condition and that disease of the aorta is not a necessary prerequisite. He states that in most of his cases the aorta was not at all, or but slightly, diseased.

Flockemann,[4] 1898, published twenty-two cases and came to the conclusion that dissecting aneurysm is not due to disease of the vessel

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* From the Department of Pathology, Stanford University Medical School.

1. Peacock, T. B.: Report on Cases of Dissecting Aneurysm, Tr. Path. Soc. London **14**:87, 1863.

2. Moosberger, Walter: Zur Symptomatologie des Aneurysma dissecans, Schweiz. med. Wschnschr. **5**:325, 1924.

3. Boström, E.: Das geheilte Aneurysma dissecans, Deutsch. Arch. f. klin. Med. **42**:1, 1887.

4. Flockemann: Ueber Aneurysma dissecans, München. med. Wchnschr. **45**: 847, 1898.

wall and only in exceptional cases is it due to trauma. He believed that the introductory tear in the inner layers results from stretching of the aorta following overaction of an hypertrophied left ventricle.

Schede,[5] 1908, summarized the cases reported since the time of Flockemann. His interpretation of the etiology of the disease appeals to the reason far more than does that of Flockemann. Schede held the view that dissecting aneurysm depends on the same factors as do aneurysms in general. He considered the strong elastic layer of the media the most important one in the vessel wall. Numerous small tears of the elastic fibers occur in the media owing to the disease; finally the vessel wall can no longer withstand the pressure of the blood, and the wall tears. He also considered that trauma may constitute a single great injury which may cause an aneurysm to develop when there is little existing disease of the vessel. Trauma also may be, and often is, the factor which causes the already diseased vessel to tear. Schede analyzed the cases of Boström and Flockemann and found, in his opinion, evidences of disease of the vessels in most of the cases.

Other investigators than Schede have stressed the importance of degeneration of the elastic fibers of the media as an etiologic factor in dissecting aneurysm. Babes and Mironescu,[6] in 1910, described a peculiar case in which disease of the vessel wall had caused a separation of the layers before the intima was broken due to degeneration of the media. They found fatty degeneration, calcification, areas of round cell infiltration, hemorrhage and granulation tissue mainly confined to the media. This condition they believed forms an independent disease of the media which they have called mesarteritis dissecans. Moriani,[7] Krukenburg [8] and Whitman and Stein [9] have reported somewhat similar cases.

The relation of trauma to the development of dissecting aneurysm is emphasized by an observation of Rolleston's.[10] In 1893, he presented a case in which in a stableman, 45 years of age, a dissecting aneurysm had been caused by the kick of a horse. The aneurysm was

5. Schede, Franz: Beiträge zur Aetiologie, Verlauf und Heilung des Aneurysma dissecans der Aorta, Virchows Arch. f. path. Anat. **192**:52, 1908.

6. Babes, V., and Mironescu, T.: Ueber dissezierende Arteriitis und Aneurysma dissecans, Beitr. z. path. Anat. **48**:221, 1910.

7. Moriani, G.: Ueber einen Fall von Aneurysma dissecans Aortae Berücksichtigung der frischen Rupturen, Virchows Arch. f. path. Anat. **202**:283, 1910.

8. Krukenburg, E.: Beiträge zur Frage des Aneurysma dissecans, Beitr. z. path. Anat. u. z. allg. Pathol. **67**:329, 1920.

9. Whitman, R. G., and Stein, Herman B.: A Contribution to the Pathogenesis of Dissecting Aneurysm: A Case of Dissecting Mesaortitis (Babes and Mironescu) Without Dissecting Aneurysm, J. M. Res. **44**:579, 1924.

10. Rolleston, H. D.: Traumatic Dissecting Aneurysm of the Aorta, Tr. Path. Soc. **44**:38, 1893.

located just above the aortic valve, extending to the scar of the ductus arteriosus. A second aneurysm had formed in the thoracic aorta. The patient died on the fourth day. The aorta showed only slight atheroma. Instances of this kind make it evident that trauma is a factor with which we must reckon.

A number of investigators have pointed out the importance of arteriosclerosis as a contributing cause in the production of dissecting aneurysm. MacCallum,[11] 1909, reported five cases in which the aorta was the seat of marked arteriosclerosis. One of these aneurysms, pictured in his textbook, extended from just above the aortic valve to the iliac arteries and was lined throughout by endothelium. In the eighty cases collected by Peacock, forty-two patients had arteriosclerosis, fifteen had dilatation of the aorta, two had congenital malformation of the arteries, eleven apparently had sound vessels.

Kaufmann[12] believes that the most common cause of dissecting aneurysm is arteriosclerosis. Through stretching, the inner coats are ruptured or an atheromatous area breaks through. He recognizes also that trauma is often responsible since the condition occurs, at times, in children 14 and 15 years of age.

In the great majority of cases, dissecting aneurysm results in death within a few hours or a few days. This is due to the fact that the sac commonly ruptures into the pericardium (about 50 per cent) or into the left pleura, mediastinum, etc. In the relatively few cases in which the sac again opens into the aorta there may result a so-called "healed" aneurysm. The sac becomes covered with endothelium, and the patient often lives for years. These patients usually develop marked hypertrophy of the left ventricle. They suffer from palpitation, dyspnea, epigastric pain and cardiac weakness. Among Peacock's collected cases of dissecting aneurysm are five that had healed. The patients had lived nine months, one year,[13] eight years, eleven years and eighteen years(?), respectively, after the tear in the aorta had occurred. In all five cases the heart was hypertrophied and dilated. Boström's eighteen cases of healed dissecting aneurysm have already been mentioned. According to Resnik and Keefer,[14] approximately fifty cases of the healed type have been reported in the literature; some of these have been accidental discoveries at necropsy.

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11. MacCallum, W. G.: Dissecting Aneurysm: Report of Five Cases, Bull. Johns Hopkins Hosp. **20**:9, 1909.

12. Kaufmann, E.: Spec. path. Anat. **1**:107, 1922.

13. This is more properly a case of anomaly of the aotra since there were two aortae running the entire distance to the iliacs. The heart was very large, with great hypertrophy and dilatation of the chambers.

14. Resnik, W. H., and Keefer, C. S.: Dissecting Aneurysm with Signs of Aortic Insufficiency, J. A. M. A. **85**:422, 1925.

The following case report illustrates the extreme hypertrophy of the heart which may result from a healed dissecting aneurysm of long standing.

REPORT OF CASE

History.—J. G. G., a salesman, aged 32, married, was admitted to Lane Hospital, Feb. 19, 1925, complaining of a cold and cough which had persisted for two months and extreme shortness of breath which had been present for one week. He said that he had had heart trouble since 1910. This was associated with a sense of fulness in the epigastrium which had troubled him intermittently since then.

He had had mumps, measles, scarlet fever, pneumonia and diphtheria, the last shortly after his heart trouble in 1910. He said that he had had tonsillitis almost every year from boyhood until 1919, when his tonsils had been removed. His gallbladder was taken out in 1922. In 1917, he had had gonorrhea, which he said was cured in about three months. There was no history of syphilitic infection.

In 1910, the patient had run a mile race. Two days later, he had felt a colicky pain in the epigastrium which was so severe that he had called a physician. The physician had discovered what he had interpreted as a serious valvular disease of the heart. He had ordered the patient to remain in bed. He was at that time living in the country. Later he had come to San Francisco, where he was seen by specialists, who had advised bed rest for six months, believing also that he had valvular disease. The patient had followed this advice. On return of his strength, after this period of rest, he found that he could engage in almost any kind of physical exercise, such as swimming, riding, speedway automobile racing, etc., without cardiac distress.

Except for occasional attacks of indigestion and gaseous eructations, he had been well until 1917. In that year he had had several attacks of what had been thought to be biliary colic. As these attacks continued, his gallbladder had been removed in 1922. Indigestion had continued intermittently, occasionally accompanied by pain in the left lower quadrant of his abdomen. He had not experienced any symptoms referable to his heart, except occasional palpitation and feeling of pressure from gas, which often accompanied the abdominal pain. He had obtained relief from gas pains by taking tablets of nitroglycerine, 0.01 Gm. From January, 1924, to the time of his admission to the hospital in February, 1925, he had been taking daily 100 of these tablets.

In December, 1924, he had taken cold, which had persisted until the middle of February, when he had had an acute exacerbation. Since February, the patient had been unable to sleep at night and had had periods of acute indigestion with colicky pain in the abdomen. About one week before admission to the hospital, he had become extremely short of breath. Three days before admission, his legs had become swollen for the first time. He had experienced sharp pains in the legs when walking. These had disappeared following rest. He had not been bedridden before coming to the hospital.

Examination.—This revealed that his eyes and ears were normal. His lips and cheeks were slightly cyanotic. Venous pulsation was visible in the vessels of the neck. There was some impairment of the percussion note at both bases posteriorly, and crepitant râles were heard over these areas.

His heart was greatly enlarged. The point of maximum impulse was seen and felt in the eighth intercostal space in the midaxillary line. His pulse rate was regular. The pulse was full, of the Corrigan type. The pulse rate was about 65 a minute. The dominant murmur was diastolic. It was heard loudest over the

sternum at the junction with the second interspace on the left. This murmur was transmitted all over the precordium and into the neck. A short, soft, systolic murmur was heard at the apex and was transmitted to the axilla. In addition there was a low, soft, rumbling systolic murmur over the precordium. This was thought to be due to roughening of the aortic valves. The Duroziez sign was positive. The blood pressure was 140 systolic and 10 diastolic, making a pulse pressure of 130.

The liver was enlarged and tender, reaching to the umbilicus in the midline. The spleen was not palpable. Except for an old laparotomy scar, the abdomen was normal. A slight enlargement of the inguinal lymph nodes was present. The reflexes were hypo-active but equal throughout. The extremities showed slight edema; the finger-nails were markedly cyanotic.

Treatment and Course.—The patient was kept in bed and given tincture of digitalis, theocin and nitroglycerine. His fluid intake was restricted. In a few days he felt much better. The edema had subsided, his liver had become smaller and less tender. A slight cough persisted, and râles continued to be heard over the chest.

While the patient was in the hospital, his temperature ranged from 36.2 to 37 C. (96.7 to 98.6 F.). His respirations varied from 20 to 24 per minute, except at the time of entry, when they had been 30. The pulse rate varied between 60 and 80 per minute.

The hemoglobin content of his blood was 90 per cent (Dare). The white cells numbered 6,000 per cubic millimeter. The differential count was normal. His urine was of a cherry-red color, owing to an abundant deposit of urates. A faint trace of albumin was found but no sugar. The Wassermann reaction of the blood was negative. Roentgenologic examination of the chest showed a marked enlargement of the heart in the aortic type, enlargement of the root of the aorta and passive congestion of the lungs. The patient was dismissed on March 15, 1925, very much improved.

Second Admission.—On June 15, the patient reentered the hospital in a state of extreme dyspnea and with moderate edema of the extremities. He had been taking tincture of digitalis, 15 minims (0.92 cc.), three times a day, since leaving the hospital. One week before the present entry this had been increased to 20 minims (1.25 cc.) four times daily. He had also been taking large doses of salts daily.

Examination at this time revealed marked dyspnea, with little cyanosis and moderate edema. The pulse rate was about 80, and the pulse was definitely alternating in type. There was some congestion at the bases of the lungs. The liver was palpable but not tender. By July 2, the dyspnea had diminished, but edema of the legs, ankles, thighs and scrotum had increased. On July 11, he began to cough, and from then on he became rapidly worse. He was dyspneic at all times. Opiates were required to give him any rest. His pulse had become irregular. His condition became progressively worse until his death on Aug. 2, 1925.

Clinical Diagnosis.—Valvular disease of the heart; aortic insufficiency; mitral insufficiency; aortitis.

Anatomic Diagnosis.—Open ductus arteriosus; aneurysm, dissecting, healed, of arch of the aorta; operation, cholecystectomy, healed; fatty liver.

Summary of Necropsy Record.—The body was that of a fairly strongly built man of about 35 years. There was marked cyanosis of the lips, ears and fingers The abdomen was distended. An old laparotomy scar was found to the right of

the umbilicus. The face was moderately edematous, the scrotum, genitals and legs markedly so. The peritoneal cavity contained no fluid. The colon and stomach were distended with gas. The diaphragm was at the fifth interspace on both sides. The chest was rather flat, and the right side was moderately larger than the left. The pleural cavities were empty and free from adhesions.

The heart was about three times normal size; it weighed 860 Gm. The enlargement was due principally to the enormous dilatation and hypertrophy of the left ventricle. The right auricle was moderately dilated, and the wall was thickened. In the right auricular appendage, there was an antemortem blood clot. Immediately above the right auricle, the dilated aorta formed a large aneurysmic sac about the size of a man's fist. The right ventricle was slightly dilated; its wall was about twice the normal thickness (5 mm.). The tricuspid valve was normal. The left auricle was also dilated and thickened. The left ventricle was tremendously dilated and hypertrophied. Its wall averaged between 18 and 20 mm. in thickness. The papillary muscles and chordae tendinae showed marked hypertrophy. This is clearly shown in figure 1. The mitral orifice was dilated and admitted three fingers. The flaps of the valve were somewhat enlarged and thickened. The aortic ring was somewhat stretched, its circumference measuring 11 cm. The aortic valve was otherwise normal.

The aneurysmic sac mentioned above began about 1 cm. above the aortic valve. As shown in figure 1, it was demarcated from the aorta below by a sharp ridge formed by a circular tear from which the inner part of the tube had retracted. The sac extended upward to the beginning of the horizontal part of the arch and there ended abruptly. On close examination, there was found on the right anterior side of the inner surface of this sac a flattened tubular passage about 3 cm. in diameter, which communicated widely with the aneurysmic sac below. This tube ascended along the inner surface of the sac and was continuous with the transverse and descending portions of the aortic arch. As may be seen in the photograph, figure 1, the innominate artery (*c*) on the right and the carotid and subclavian arteries (*a* and *b*) on the left are given off directly from the upper portion of this flattened tube which represents the inner layers of the base of the aorta. The lower end (*e*) where the probes can be seen projecting was originally continuous with the ridge which can be seen immediately above the aortic valve. In the arch of the aorta near the opening of the ductus arteriosus a second annular tear had occurred in the inner layers of the aorta by which the blood from the aneurysmic sac was returned to the aorta proper. It is evident that practically the entire volume of blood passed from the left ventricle into the aneurysmic sac and thence into the aorta in the transverse portion of the arch at about the level of the ductus arteriosus. By means of a short back flow from this point, some of the blood was able to enter the openings of the innominate, carotid and subclavian arteries.

The sac itself was lined completely with endothelium. The surface was slightly uneven, and showed a moderate amount of longitudinal wrinkling. There was only an occasional small yellow spot, and on the whole little evidence of atheromatous change. Running transversely across the sac on a line that fell between the ridge (fig. 1, *d*) and the lower end of the aorta, was a slightly thickened band of intima which measured 0.5 cm. in width between the ridge and aorta and widened to 1.5 cm. on the wall of the sac. It seems probable that the aorta ruptured in two places at approximately the same time, so that a ring of aorta was carried away as part of the sac wall, becoming thin as the wall stretched.

The probe (*f*, fig. 1) passed through an open ductus arteriosus which measured about 3 mm. in diameter at its narrowest part. It was at about this point that the blood reentered the aorta.

PLATE 1

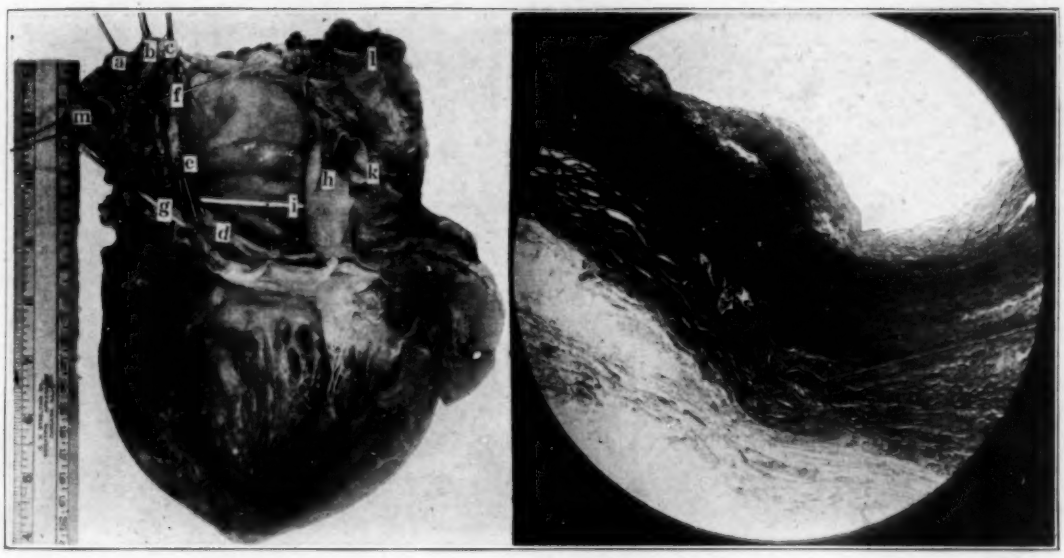

Figure 1

Figure 2

Fig. 1.—Heart with left ventricle and aneurysmic sac exposed; *a*, left subclavian artery; *b*, left common carotid artery; *c*, innominate artery; *d*, tear in aorta above aortic valve; *e*, torn end of ascending aorta; *f*, probe passing through open ductus arteriosus; *g*, probe in left branch of pulmonary artery; *h*, piece of wall removed for section; *i*, probe holding walls of sac apart; *k*, left branch of pulmonary artery; *l*, trachea; *m*, cork in the transverse aorta.

Fig. 2.—Photomicrograph of portion of wall of aneurysmic sac; Weigert's elastic fiber stain and Van Gieson (low power magnification). Fibrous tissue of irregular thickness makes up inner third of wall. The dense fibrous middle portion represents all that remains of the media, which has completely lost its elastic tissue. The adventitia is greatly thickened and composed largely of hyaline fibrous tissue.

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The lungs had no scars at the apexes. Areas of consolidation were not found, but signs of chronic passive congestion. The spleen also showed passive congestion. Several small accessory spleens were present at the hilum. The suprarenals and kidneys were normal.

The thoracic spine was not eroded by the aneurysm. The stomach and duodenum contained a large amount of black fluid. The mucous membrane of the stomach was thin and contained numerous small hemorrhages.

The liver was small. The tissue was firm and showed a moderate cyanotic atrophy. The thoracic and abdominal portions of the aorta were normal except for an occasional small yellow spot in the intima.

The small and large bowel were filled with a large amount of greenish-black fluid.

Histologic Examination.—Section of Aorta Through Tear Above Aortic Valve: In the part of the aorta forming the wall of the sac for a width of about 1 cm. above the tear, the intima was replaced by a layer of partly hyaline fibrous tissue which near the tear was very thick. Weigert's elastic fiber stain showed a complete absence of elastic tissue in this area. The inner layers of the media were fibrous, while the outer third was completely necrotic and hyaline and contained many small cracks and fissures. This part merged gradually with the hyaline fibrous tissue of the adventitia. The elastic tissue of the media consisted of a few scattered groups of fine fibrils which under high power magnification appeared short and fragmented.

The adventitia was considerably thickened. Approximately the inner half of it was necrotic and hyaline. The outer part was composed partly of hypertrophied smooth muscle and partly of hyaline fibrous tissue. There was a moderate diffuse round cell infiltration. The walls of the vasa vasorum were moderately thick and showed a beginning hyaline degeneration.

The aorta immediately below the tear was covered by an intima which showed only moderate fibrous thickening. The internal elastic membrane was fairly well preserved. The muscle of the inner two-thirds was well preserved, showing here and there some areas of hydropic degeneration. The outer third was partly hyaline and in places necrotic.

The sections included part of the wall of one of the sinuses of Valsalva. Here the intima was very thin; otherwise the section was practically the same as described above.

Wall of Aneurysmic Sac: A section taken from the wall of the sac at *h*, figure 1, showed a wall of irregular thickness which on the average was slightly thinner than that of the normal aorta. The inner surface was covered by a layer of moderately cellular fibrous tissue of variable thickness. The media was about one-third normal thickness and entirely fibrous. Weigert's elastic tissue stain revealed a complete absence of elastic fibers. The adventitia was relatively thick though irregularly so. It was composed almost entirely of hyaline collagen fibrils containing only a few scattered cells (fig. 2).

Thoracic Aorta: There was only slight fibrous thickening of the intima and a few areas of hydropic degeneration in the muscle. The elastic fibers were practically normal except for occasional small areas in which they were reduced in numbers or absent. A slight perivascular round cell infiltration was present in the adventitia.

The innominate and carotid arteries showed nothing unusual except a slight irregular thickening of the intima and moderate perivascular round cell infiltration of the vasa vasorum. The elastic tissue apparently was normal.

Heart Muscle: The muscle fibers showed marked diffuse hypertrophy. The pericardium was slightly and diffusely infiltrated with round cells.

Liver: The liver cells in the centers were much atrophied, and the capillaries between them were widely distended. Much fat in the form of fine droplets was present in the remaining liver cells in the periphery of the lobules.

Lung: The pulmonary tissue was partly collapsed; in other places it was emphysematous. The capillaries were distended with blood. The septums were distinctly thickened in many areas, and showed an increase of fibrous tissue. A moderate number of pigmented phagocytic cells were present in the alveoli.

COMMENT

It is evident from the brief review of the literature submitted at the beginning of this report that at least three factors are concerned in the production of dissecting aneurysm. These factors may be stated as follows: (1) disease of the vessel wall; (2) trauma, including external violence, lifting of heavy weights, endurance tests, temporary rises in blood pressure due to emotional states of fear, anger, etc.; (3) congenital malformation with weakness of the vessels.

In our case there is only slight disease of the vessels, not enough to make it clear that this played any real part in the etiology. The lesion in the aorta followed closely on a marked strain placed on the arteries in consequence of a mile race. There was also present a congenital anomaly in the form of an open ductus arteriosus. The open ductus was funnel-shaped, measured about 8 mm. in diameter on the aortic side, narrowing to about 3 mm. at its opening into the pulmonary artery. An open ductus of only 3 mm. in diameter probably had little direct influence in the production of the aneurysm. The fact that the ductus failed to close, however, indicates some inherent or congenital abnormality of the vessels. That intrinsic weakness played a part in the production of the aneurysm is likely, since thousands of young men at 17 run mile races without any serious consequences. This young athlete had performed similar feats on other occasions. He had, at least, subjected his circulatory apparatus to many stresses and strains of a similar nature, because he informed me during his first stay in the hospital that he had participated often in swimming, boxing, racing and other competitive sports. It was probably the accumulated effect of repeated trauma of this type plus congenital weakness of the vessels that brought on the partial rupture of the aortic wall during the mile run.

An unusual feature of the case is the fact that the aneurysm produced in 1910 had "healed" so completely that the man lived for fifteen years afterward. Not only that, but he was able to compete in athletic sports. Participation in such events caused him no undue cardiac distress. Furthermore, he was able to withstand the shock of several infectious diseases and of two surgical operations. Following his cardiac crisis he had diphtheria, mumps, influenza and several attacks of tonsillitis.

He had a tonsillectomy performed in 1919, and his gallbladder was removed in 1922. Although the diagnosis of aneurysm had not been made at the time of the accident, nevertheless, the best possible treatment was given the patient. During the six month's rest in bed, the heart and vessels adjusted themselves to the new condition. The compensation was so complete that the circulatory system withstood stresses considered severe for a normal heart. The result had been an enormous hypertrophy and dilatation of the left ventricle. This case illustrates remarkably well the flexibility and compensating power of the cardiovascular system.

In tears near the aortic valve, the aortic ring is likely to be stretched. In my case the aortic ring measured 11 cm. in circumference, and there was certainly more or less regurgitation of blood into the left ventricle. All clinical signs pointed to the existence of an aortic insufficiency. The patient had a Corrigan type of pulse and a positive Duroziez sign. A diastolic murmur could be heard best over the second intercostal space on the left, and it was transmitted over the whole precordium and into the neck. His heart was enlarged to the left.

SUMMARY

A case is presented of a dissecting aneurysm which developed in the aorta of a young man 17 years old, following a mile race. The man lived fifteen years afterward and was able during this time to compete in strenuous athletic events.

A patent ductus arteriosus of small caliber was also present.

During the last years of life, all signs of aortic insufficiency could be made out. At necropsy the heart was found to be enormously enlarged, mainly due to hypertrophy and dilatation of the left ventricle.

The tear in the aorta had occurred immediately above the aortic valve, where a sac-like aneurysm the size of a man's fist had formed in the walls of the ascending aorta.

Laboratory and Technical Notes

CULTURAL METHODS FOR INCREASING THE NUMBER OF SPIROCHAETAE PALLIDAE IN FRESH SYPHILITIC TISSUE *

LOREN W. SHAFFER, M.D.
DETROIT

The object of this study was to elaborate a cultural method by which the number of *Spirochaetae pallidae* could be increased in excised tissues in order to demonstrate the organisms more readily, especially in the lesions of late syphilis, such as aortitis. The study was undertaken following an attempt to discover the sources of error and to improve the methods of impregnating *Spirochaeta pallida* with silver in the tissues. The effects of chemical impurities in the cheaper grades of formaldehyde, its hydrogen ion concentration and refined methods for its dilution were investigated without any spectacular results. The time elapsing between the patient's death and the fixation of suspected syphilitic tissue has been considered as a cause of failure to demonstrate *Spirochaeta pallida*. While the rate of disappearance of spirochetes from fresh syphilitic tissue was being determined, interesting observations were made which led to the various experiments herein reported.

Fresh tissue susceptible to syphilis from man, monkey and rabbit, should offer an ideal pabulum for the culture of *Spirochaeta pallida*, and at the same time supply the anaerobic conditions necessary for their growth. Fresh tissue is frequently employed in anaerobic culture mediums to aid anaerobiosis. Noguchi [1] believed that the use of fresh renal tissue of the rabbit was one of the essentials in his first successful culture of this organism. When removed from the body the tissue is probably freed from the immune bodies elaborated by the host which tends to keep local multiplication of organisms under control. This is not proved in the present paper, and immune bodies may offer a stumbling block in the application of this work in late processes. It would therefore appear logical that incubation of the tissue itself should offer a simple and valuable means of increasing the number of *Spirochaetae pallidae*.

Chancres in rabbits were used as a readily available source of material rich in *Spirochaetae pallidae*. The technic of intratesticular inoculation and transfer, as described by Brown and Pearce,[2] was

* This work was carried out in the Section on Dermatology and Syphilology, Mayo Clinic.

1. Noguchi, Hideyo: A Method for the Pure Cultivation of Pathogenic Treponema Pallidum (Spirochaeta Pallida), J. Exper. Med. **14**:99-108, 1911.

2. Brown, W. H., and Pearce, Louise: Experimental Syphilis in the Rabbit, J. Exper. Med. **31**:475-498, 1920.

adhered to. A strain of *Spirochaeta pallida* was employed which produced marked primary syphilitic orchitis with, at times, the development of scrotal chancres after an average incubation period of thirty days (Nichols' strain [3]).

Spirochetosis of rabbits,[4] due to *Spirochaeta cuniculi,* was guarded against by careful examination and selection of the animals. This contamination was further ruled out because of the deep and nodular character of the orchitis which was induced, the longer incubation period, the occasional development of late secondary lesions and the successful transfer of the infection by inoculation of emulsified lymph nodes and whole blood.

TECHNIC

A rabbit presenting a well developed chancre of the testis, positive on dark-field examination was killed with chloroform. The hair of the scrotum and surrounding area was clipped, the skin bathed with 50 per cent alcohol and dried, and the testis removed by cutting cautery and immediately singed in the flame. Under aseptic technic the uninfiltrated portion of the testis was removed and discarded. The indurated portion was cut radially into blocks of equal size, at least 5 mm. in each dimension. The average chancre made from four to six such blocks. These blocks were put through various procedures while in the fresh state, and then fixed in neutral formaldehyde and stained by the silver impregnation method of Levaditi for *Spirochaeta pallida.* In certain cases the block, after such procedures, instead of being fixed and stained, was macerated for dark-field examination, or injected into the testes of normal rabbits as a test for pathogenicity. In all cases one representative block from each chancre was fixed at once and stained as described, and sectioned for comparison with those subjected to the procedures.

EFFECT OF TIME INTERVALS AND VARYING TEMPERATURES ON NUMBER OF SPIROCHAETAE PALLIDAE REMAINING IN FRESH TISSUE

Portions of fresh chancre tissue were placed in sterile Petri dishes and permitted to stand at room temperature for varying periods. These specimens were fixed, stained and sectioned at intervals of one hour, from one to eight hours after the specimen had been obtained. There was no recognizable change in the number of spirochetes as compared with sections from the original block. Specimens were then compared four times during periods of from eight to twenty-four hours, with the same result. It was thus evident that *Spirochaeta pallida* did not disappear rapidly from even small blocks of fresh tissue.

In the next procedure, the Petri dishes were sealed with adhesive plaster to prevent desiccation and to permit longer incubation of the

3. Nichols, H. J.: Observations on a Strain of Spirochaeta Pallida Isolated from the Nervous System, J. Exper. Med. **19**:302-371, 1914.

4. Noguchi, Hideyo: A Note on the Venereal Spirochetosis of Rabbits. A New Technic for Staining Treponema Pallidum, J. A. M. A. **77**:2052-2053, 1921.

blocks. At the same time, it was decided to study the influence of temperature, as well as of time, by arranging parallel series of experiments. Blocks were placed in the incubator at 37 C., and in the icebox, as well as at room temperature.

Comparative Results of Incubation at Different Temperatures and for Varying Periods

Hours	Incubator	Room Temperature	Icebox
0	+	+	+
24	++	+	+
40	++	..	..
48	+++	+	+
64	+++	..	..
72	++++	±	±
90	++	..	..
96	++	..	..

The sign + indicates the number of Spirochaetae pallidae in specimen fixed at once or equivalent numbers; ++, +++, ++++, approximate increase in the number of Spirochaetae pallidae as compared with the original specimen; ±, less than in the original specimen but Spirochaeta pallida still present.

For this comparison the number of spirochetes appearing in the fresh tissue, fixed immediately after removal from the rabbit, was adopted as the standard and rated as +. The number of the + signs indicates the multiple found on subsequent examinations. The results as charted are only approximate as it is obviously impossible to express them numerically.

The incubator experiments were repeated several times and the results totaled and averaged, since there may be great variation in the number of organisms in different portions of the same chancre. An attempt was made to photograph sections to show the relative increase, but oil immersion photographs did not show sufficiently large fields to be of service. Impressions could be formed only by direct examination of the slides. It was not possible to carry out the experiment satisfactorily beyond ninety-six hours on account of autolysis of the tissue. It was practically impossible to sterilize the scrotum of rabbits because of follicular and deep secondary infection in the chancre, without using penetrating sterilizing agents equally destructive to *Spirochaeta pallida*. The presence of secondary invaders, however, did not seem to interfere with the viability and growth of the spirochetes.

The results secured at room temperature and in the icebox after seventy-two hours showed that *Spirochaeta pallida* was still present, although in decreased numbers. Lacy and Haythorn [5] have shown that *Spirochaeta pallida* retains its motility in the icebox for seven days in excised chancres of man and for one hundred and twenty-one days in serum sealed in capillary tubes. My observations at refrigeration and

5. Lacy, G. R., and Haythorn, S. R.: Viability of Spirochaeta Pallida in Excised Tissue and Autopsy Material, Am. J. Syph. **5**:401-408, 1921.

room temperature were not pursued further or confirmed, because of the greater interest attached to the remarkable increase in numbers of organisms in the incubated tissues.

METHODS OF INCUBATION

Aerobic Incubation.—The unusual character of the sections from aerobically incubated tissue leaves no doubt that cultural growth occurred in situ. Thus, in some cases, particularly in the blocks incubated for from forty-eight to seventy-two hours, the spirochetes became so numerous as to form solid clumps in scattered areas. These areas could be recognized readily with low power magnification by the darkening of the tissues. Furthermore, the growth occurred in the deeper portions of the blocks where anaerobic conditions were approached. It is therefore advisable to use fairly large blocks of tissue.

The possibility of changes in reaction in this incubated tissue making *Spirochaeta pallida* more readily stainable by silver impregnation than in blocks fixed at once was considered. The Levaditi stain is a simple process of reducing silver salts and should not be affected by the presence of acid. The massing of the organisms in clumps is further evidence of growth in situ. Be this as it may, it still remains that incubated tissue is richer in demonstrable spirochetes than that fixed at once.

The spleen of syphilitic rabbits has been shown to contain *Spirochaeta pallida* even very early in the infection.[6] They are very few and difficult to demonstrate by direct dark-field examination or in stained sections. The spleen is easily removed from rabbits without contamination, and accordingly two different spleens were incubated aerobically and stained by the Levaditi method. The sections failed to show any increase in the number of *Spirochaetae pallidae*. No satisfactory explanation can be made for this, but it is considered that the small size of the rabbit's spleen may render it unsuitable for aerobic incubation.

Anaerobic Incubation.—Blocks of fresh chancre tissue were placed in test-tubes in an anaerobic Novy jar, with combined exhaustion and chemical absorption of oxygen, and incubated for varying periods. Autolysis of the tissue from secondary infection was less rapid owing to the anaerobic conditions, and incubation was continued at intervals up to twenty-one days. As in the previous work, secondary infection did not seem to interfere with the growth of spirochetes as long as the tissue remained firm. Examinations were made on the third, fourth,

6. Brown, W. H., and Pearce, Louise: A Note on the Dissemination of Spirochaeta Pallida from the Primary Focus of Infection, Arch. Dermat. & Syph. **2**:470-472, 1920.

fifth, seventh, ninth, tenth, fourteenth and twenty-first days. There were numerous *Spirochaetae pallidae* up to five days, probably twice as many as in the original specimen. From the fifth to the twenty-first day there was a gradual diminution; the twenty-one day specimen contained about the same number of organisms as the original. The spirochetes were distributed uniformly throughout the tissue; they did not predominate in the central portions as they did in the tissue incubated aerobically. They did not form in clumps or show the marked evidence of cultural growth found in the aerobic specimens. It is unfortunate that specimens were not examined at intervals of twenty-four and forty-eight hours. The anaerobic method, for long incubations at least, would not seem to offer any advantages over that of simple aerobic incubation.

Horse Serum Cultures (Anaerobic).—Culture of *Spirochaeta pallida* in mediums of the Noguchi,[1] Weiss and Wilkes-Weiss [7] and Baeslack and Keane [8] types is not difficult. It was decided to use these methods to determine the growth of spirochetes in tissue planted in these mediums. Baeslack and Weiss mediums were placed in tall test-tubes with a block of fresh chancre tissue at the bottom. Portions of fresh renal tissue from a normal rabbit were usually added to aid anaerobiasis, as advocated by Noguchi. The contents of the tube were overlaid with petrolatum and incubated for varying periods. Spirochetes grew rapidly into the surrounding mediums and were easily demonstrated within three days by direct dark-field examination. This confirms the observations of Baeslack who suggested this as a method of diagnosis. The growth in the mediums reached its maximum in from ten to twelve days and thereafter slowly decreased. *Spirochaeta pallida* was still present in those specimens not contaminated, however, for as long as two months.

The chancre tissue was removed from the tubes at varying intervals up to two months, fixed and stained by the Levaditi method and sectioned as before. There was a definite increase in the number of spirochetes in the tissue over the original. This increase was most marked for from eight to twelve days and then there was a gradual decrease, but spirochetes were still present in the tissue incubated for two months. They were diffusely scattered, being largely confined, however, to the interstitial portion of the testicular tissue.

Incubation in Buffered Solution of Sodium Chloride.—It is probable that the products of growth of the spirochetes so change the pabulum and hydrogen ion concentration as to induce conditions unfavorable for

7. Weiss, Charles; and Wilkes-Weiss, Dorothy: Study of Cultural Requirements of Spirochaeta Pallida, J. Infect. Dis. **34**:212-226, 1924.

8. Baeslack, F. W., and Keane, W. E.: The Diagnosis of Primary Syphilis by Culture, J. A. M. A. **74**:392, 1920.

continued growth. Accordingly, buffered solution of sodium chloride was selected to be tested as a medium to overcome this difficulty. This would be a better test of longevity and growth of spirochetes in tissue, since there would be no additional pabulum, and yet a fixed hydrogen ion concentration would be provided. Blocks of fresh chancre tissue were therefore placed in test-tubes, overlaid with buffered (p_H 7.4) physiologic solution of sodium chloride, sealed with petrolatum and incubated for periods of from five to seventy-eight days. The tissue was removed, fixed and stained by the Levaditi method and sectioned. The five day, seven day and eighteen day specimens showed a definite though not marked increase over the original in the number of spirochetes. The thirty-six day and seventy-eight day specimens showed approximately the same number as the original specimen.

Culture in Freshly Excised Tissues.—Testes freshly excised from normal rabbits were injected with from 1 to 3 minims of a suspension containing from 3 to 5 *Spirochaetae pallidae* for each dark field. They were incubated anaerobically, as in the original experiment, for three, four and five days, respectively. The tissue was then fixed and stained by the Levaditi method and sectioned through the central inoculated area. All sections showed dense masses of *Spirochaetae pallidae* in the inoculated area. There was no evidence of ramification or growth of the organisms through the surrounding tissue, such as had been expected. The organisms behaved very much as bacteriologic cultures do in a solid medium, with growth limited closely to colonies around the original inoculations.

Throughout this work it was repeatedly noticed that *Spirochaetae pallidae* in testicular tissue were found almost exclusively in the interstitial portions. Very few were demonstrated in the acinous portions, even in the inoculated fresh specimens just described. A new set of inoculations into normal kidney were not followed by multiplication of organisms in renal tissue as such; a few were found in the small fragments of testicular tissue transplanted by the inoculation. Similarly, in the horse serum cultures, the portions of normal kidney, which were at times used with chancre transplants to aid anaerobiasis, failed to show any spirochetes on section except in the clear, serum-lined spaces, and these were probably derived from the surrounding medium. There seems therefore to be a selective quality of the *Spirochaetae pallida* or at least a varying susceptibility of tissues to its growth.

Culture in Vivo.—It was desired to eliminate secondary infection as a factor because in its presence autolysis of tissue occurs very rapidly, even though pure cultures of *Spirochaetae pallidae* are not necessary for the diagnostic purposes of these experiments, as previously shown. In order to overcome this difficulty, it was decided to plant blocks of

chancre tissue in the abdominal wall of normal rabbits in the hope of providing a practical method of evading contamination, as well as affording a simple method of anaerobic incubation. Under anesthesia and aseptic precautions, a slit was cut in the abdominal wall and four pockets made by blunt dissection. Into each of these a block of fresh chancre tissue was placed. The skin was then sutured and sealed with collodion. Some inflammatory reaction usually occurred but in no case actual suppuration. The blocks were removed under anesthesia at intervals of eight, fifteen, twenty-one and thirty days. There was a certain amount of absorption, particularly with the longer periods, and marked adhesions developed. The tissue removed was fixed and stained by the Levaditi method and sectioned as before.

At eight days there was some increase in the number of spirochetes. It is possible that if examination had been made earlier, a more opportune time could have been reached when the number of *Spirochaetae pallidae* were at a maximum. The sections showed no evidence of secondary infection. The specimens taken after fifteen days and twenty-one days failed to show any spirochetes, while the thirty day sections were again very rich in them. The latter period corresponds to the average incubation period of the primary lesion.

This experiment offers interesting possibilities that are worthy of further investigation. These rabbits were not observed after the conclusion of the experiment for the development of syphilis. A chancre might possibly have developed at the site of each implant, or at least evidence of secondary lesions in a certain proportion of cases. It offers interesting leads to the problem of immunity, and to the question of what causes the disappearance of the spirochetes after an initial increase and then reappearance in large numbers near the time of the primary incubation period. This must be an immunity mechanism, and its occurrence in waves is thus an early example of the cycles of the infection described by Warthin.[9] There is, too, the question of the actual fate of the organisms locally in this interim. Brown and Pearce [6] have shown that the infection is already widely disseminated by this time. Whether the local organisms have entirely disappeared or are only sparse, and whether this phenomenon strengthens the theory of resting forms, are still unanswered questions.

PATHOGENICITY OF SPIROCHAETA PALLIDA IN INCUBATED TISSUE

Blocks of chancre tissue incubated both aerobically and anaerobically were macerated in a mortar with normal solution of sodium chloride. One fourth of a cubic centimeter of this suspension was injected into

9. Warthin, A. S.: The New Pathology of Syphilis, Am. J. Syph. **2**:425-452, 1918.

the testis of a healthy rabbit. The rabbits were kept in individual cages under observation for the development of chancres. If induration developed, it was investigated by dark-field examination. Only those cases were considered positive in which the presence of the typical *Spirochaeta pallida* was determined.

Tissue from aerobic incubations was inoculated into the testes of four normal rabbits after periods of incubation of one, two, three and four days. Each rabbit developed a chancre, positive on dark-field examination, except the animal which received the two day material. This rabbit died after five days from other causes. The incubation period in the positive cases was thirty-two, sixty-one and thirty-one days, respectively.

Three rabbits were inoculated with macerated anaerobic tissue which had been incubated three, five and ten days, respectively. The rabbits inoculated with the three day and five day material developed chancres after forty-five and twenty-eight days, respectively. Unfortunately, the rabbit inoculated with the ten day material died seven days after inoculation.

DISCUSSION

The experiments show that *Spirochaetae pallidae* remain in fresh tissues for long periods and are still readily stained by silver impregnation methods. Incubated tissue shows, for a time at least, an increased number of organisms. The method of choice for the application of this finding to the tissues of man as a diagnostic procedure remains to be determined. I would suggest that suspected fresh tissue be incubated aerobically for from forty-eight to seventy-two hours before fixation and staining for *Spirochaeta pallida*. If rabbits are available, two portions should be transplanted into the abdominal wall or scrotum; the one being removed in three to four days for silver impregnation and section, and the other remaining as a biologic test for syphilis, the rabbit being observed for the development of a chancre or manifestations of secondary syphilis.

It is my belief that a clinical analog of this work is to be found in the syphilitic fetus. The macerated stillborn syphilitic fetus usually shows numerous spirochetes, particularly in the liver, the mother having acted as an incubator to increase the number of spirochetes greatly in the dead fetus. The syphilitic child that dies at birth, on the other hand, may show only a few or no spirochetes, depending solely on the stage in the immunity cycle at which death occurs.

SUMMARY

Simple aerobic incubation of tissue containing *Spirochaeta pallida*, if in blocks of sufficient size, results in a marked increase in the number of spirochetes, as shown in sections stained by the Levaditi method

Their occurrence in almost solid clumps is sometimes most convincing proof of cultural growth in situ. These organisms have been shown to be pathogenic when reinoculated into rabbits five days after excision of the tissue.

More refined methods of culture (anaerobically, in horse serum, etc.) offer no advantages over simple aerobic incubation in situ in the original tissue. When the tissue is planted in a medium the demonstration of *Spirochaeta pallida* in the surrounding medium affords a rapid method of checking the findings that may be expected in the tissue.

Spirochetes were demonstrated in fresh tissue when incubated for periods as long as seventy-eight days.

The growth of spirochetes inoculated into freshly excised normal tissue does not extend rapidly throughout the tissue but tends to remain localized to the point of inoculation. In testicular tissue *Spirochaeta pallida* grows by preference in the interstitial rather than in the parenchymatous portion. Renal tissue does not seem to be a suitable medium for its growth.

Transplantation of suspected tissue into the abdominal wall of rabbits affords a method of anaerobic incubation which combats the contamination otherwise almost inevitable. After an initial increase in the number of organisms, there was a decrease, followed by their complete disappearance from the tissues by the end of fifteen days. This diminution lasts through the twenty-one day period, but by the end of thirty days the organisms had returned in great numbers. This interval corresponds to the primary incubation period for rabbits. The fate of the spirochetes in the interim is conjectural.

The method of choice for incubation in the application of these findings to the pathologic diagnosis of syphilis remains to be determined. Simple aerobic incubation and transplantation into rabbits seem worthy of trial.

805 Kresge Building.

General Review

RICKETTSIAE AND DISEASE*

E. V. COWDRY, PH.D.
NEW YORK

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HISTORICAL INTRODUCTION

"Rickettsia" is the generic term suggested by da Rocha-Lima in 1916 for certain small micro-organisms which occur in lice. It was given in memory of Howard Taylor Ricketts, who died in 1910 of typhus fever in Mexico City while investigating its etiology. The specific designation *"prowazeki"* was added to perpetuate the name of another investigator, von Prowazek, who gave his life in the study of the same disease.[1] Strong evidence is now available that typhus fever

* From the Laboratories of the Rockefeller Institute for Medical Research.

1. Typhus fever has exacted a heavy toll among physicians and nurses, and many other investigators have sacrificed their lives in order that knowledge concerning it may be increased, of whom may be mentioned: Bacot, Conneff, Cornet, Jochmann, Luthje, Schüssler and Weil.

is caused by *R. prowazeki,* and this organism must be regarded as the type species with which all other "rickettsiae" are to be compared. Failure to observe this convention has resulted in much confusion in the literature.

It was also in 1916 that Töpfer reported the discovery of a second rickettsia in lice, which had been collected from soldiers suffering with trench fever. This organism is commonly referred to under two names: (1) *R. wolhynica,* to indicate the area in the Eastern front, where German investigators first recognized the disease, and (2) *R. quintana* (Schminke), to emphasize its association with a five-day fever. Bacot (1921), Wolbach, Todd and Palfrey (1922), and others believe it to be identical with *R. pediculi*—an organism which da Rocha-Lima thought to be a normal inhabitant of the louse and altogether unassociated with disease. In accordance with what has become the usual practice, da Rocha-Lima gave this rickettsia the specific designation "pediculi" in consideration of its host, *Pediculus humanus.*

A third rickettsia was found to be associated with Rocky Mountain spotted fever by Ricketts (1909), whose investigations have been confirmed and greatly extended by Wolbach (1917, 1919). This organism has been called by Wolbach *Dermacentroxenus rickettsi,* stress being placed on the genus of the tick which harbors it and on its discoverer. Although the generic term is "dermacentroxenus," instead of "rickettsia," and the parasite possesses certain special characteristics, as, for example, an intranuclear phase, it is, nevertheless, grouped among the rickettsiae, owing to its close general resemblance to the members of this ill-defined genus.

In 1923, Sellards reported the cultivation on artificial mediums of a fourth rickettsia from animals experimentally infected with tsutsugamuchi disease, a fatal fever occurring during the summer months in certain parts of Japan. The condition is also called "Japanese River sickness," because the disease occurs when certain rivers on the western coast of Japan, fed by the spring rains, overflow their banks. It is caused by the bites of infected mites (*Trombicula akamuchi*). According to Sellards, the term "tsutsugamuchi" signifies "dangerous bug." To indicate its geographic localization, he called the organism, *R. nipponica.*

More recently, a fifth rickettsia has been described by Cowdry (1925, *c, d*) in cases of heartwater, which is, on the other hand, a disease restricted to animals (sheep, goats and cattle), hence the name *R. ruminantium.* It is confined to South Africa, where it is of great economic importance, owing to the high mortality caused by it. The term "heartwater" is applied to the disease on account of the hydropericardium often observed at necropsy.

These five diseases possess certain features in common. They are all transmitted by blood feeding insects or arachnids, exhibit a fairly

high fever, and one attack confers an immunity in the survivors lasting several months, as in trench fever, or for a period of years, or for life. There is invariably more or less involvement of the nervous system and the development of an exanthem in all, with the single exception of heartwater. The degree of resemblance between the different rickettsiae will be mentioned in detail subsequently. It has been suggested that they constitute, with certain nonpathogenic rickettsiae, a hitherto unrecognized group of minute organisms, distinct from bacteria (da Rocha-Lima, 1916, *b*). Some claim that they are more closely related to the "chlamydozoa" of Prowazek (Sikora, 1921) and the "strongyloplasmata" of Lipschütz (Jungmann, 1916, and Sikora, 1918). The latest work, however, tends to emphasize their bacterial affinities.

The literature is scattered but extensive. With the exception of Ricketts' pioneer researches, it is all of recent date, extending backward only about a decade. The chief factor in its rapid growth was the demand for information with which to combat typhus fever and trench fever in the World War. Useful reviews have been published;[2] but there has been no attempt to summarize all the literature on the subject. In striving to attain this end, within the limits of the space available, it is necessary to concentrate on the rickettsiae themselves as organisms capable of direct observation, and to discuss pathologic conditions only so far as they may furnish direct data regarding the nature of the rickettsiae. The viruses of the diseases mentioned have been under intensive study for years. Four of them are probably identical with rickettsiae, so that in presenting a summary of our knowledge of rickettsiae the properties of the viruses should logically be considered with equal completeness. This would, however, necessitate an extensive excursion into the field of immunology, with an analysis of literature over a period of fifty years or more, whereas the rickettsiae themselves, considered as morphologic entities, constitute for the present at least, while they remain, with but few exceptions, uncultivatable, a problem in cytology and may best be treated in this light.

GENERAL PROPERTIES OF RICKETTSIAE

In addition to the five species of rickettsiae already mentioned, thirty-nine others, which are apparently nonpathogenic, have been described. Before attempting to state the criteria which should be considered prerequisite to the inclusion of an organism in this group, brief reference may be made to certain general properties of rickettsiae.

2. Jungmann (1919), Strong (1919 *a*, *b*), Wolbach, Todd, and Palfrey (1922), Salvioli (1923), Weigl (1924, *a*), Arkwright (1924), and Wolbach (1925) See also editorial J. A. M. A. **85**:1563, 1925.

Morphology.—They are smaller than most bacteria, being generally less than half a micron in diameter. They usually occur in the form of cocci and of short bacilli, but filamentous rickettsiae are often encountered, particularly in their arthropod hosts. The shorter forms are disposed characteristically in pairs end to end.

Staining Reactions.—By ordinary methods they stain less intensely than the majority of bacteria, and their outlines are less sharply defined. They are generally colored blue by Giemsa's stain, after Zenker fixation, as advised by Wolbach (1919). Since they occur so sparingly in human tissues, it is not practicable to study them by the smear method, but in arthropods this is usually accomplished without difficulty. In smears multiplicative phases of rickettsiae may often be found (table 3) in which there is a greater interval between two individuals comprising a pair than is ordinarily met with in the case of bacteria. This interval is frequently occupied by an intermediate substance which is colored red by the method of Giemsa. A few rickettsiae exhibit chromatoid granules (see, particularly, Epstein, 1922); all are gram-negative, but some hold the stain longer than others.

Motility.—When examined by dark-field illumination, it is often difficult to distinguish them from mitochondria, unless they are very abundant, and there is but slight admixture of cellular débris. Some of the filamentous rickettsiae occurring in the bed-bug are definitely motile (Hertig and Wolbach, 1924). This is, however, a special case, no other instances being on record, although they probably occur.

Cultivation.—Attempts to cultivate the more typical rickettsiae on artificial mediums have failed in the hands of most investigators; but the bacterium-like *R. melophagi* of the sheep ked has been grown by Nöller (1917, *a*), by Jungmann (1918), by Nöller and Kuchling (1923), and by Hertig and Wolbach (1924). The cultivation of *R. rocha-limae* of the louse, which is also bacterium-like in its appearance, has been reported by Weigl (1921). The status of *R. nipponica*, cultivated by Sellards (1923), remains to be determined.

Resistance to Physical and Chemical Agents.—Any generalization is premature, but in this respect, also, some rickettsiae differ markedly from others. The viruses of typhus (da Rocha-Lima, 1919 *b*), Rocky Mountain spotted fever (Wolbach, 1919) and heartwater are easily inactivated by heat, desiccation, and chemical agents, while the trench fever virus is much less susceptible (Byam and Lloyd, 1919; Bruce, 1920).

Host Specificity.—Like other symbiotic micro-organisms, the rickettsiae are highly specific for their several hosts. No case is known in which the same rickettsia normally inhabits two species of arthropods; but other ticks, in addition to *Dermacentor venustus*, are

capable, under experimental conditions, of transmitting the virus of Rocky Mountain spotted fever (Maver, 1911; Parker, 1923). Moreover, *R. prowazeki* may develop in *Pedicinus longiceps*, as well as in *Pediculus humanus* (Arkwright, Bacot and Duncan, 1919; Atkin and Bacot, 1922); and the virus of trench fever may be transmitted by *Pediculus capitis* in addition to *Pediculus corporis* (British Trench Fever Commission, Byam, 1919), while the rickettsiae of cat fleas may be grown (Sikora, 1920) artificially in the coelom of the human louse. Attempts to infect *Pediculus humanus* with the rickettsiae of the dust louse failed (Sikora, 1920).

Hereditary Transmission.—Most rickettsiae are transmitted to successive generations through the eggs of their vectors, but *R. prowazeki* and *R. quintana* are probably not, and *R. ruminantium* is unquestionably an exception.

Filtrability.—Experiments have been made only with the pathogenic rickettsiae, the filtrates being tested, not morphologically for rickettsiae, but physiologically for the presence of active virus. There has been much difference of opinion concerning all of them. According to Olitsky (1917, 1922, *b*), the virus of typhus fever will not pass through Berkefeld V and N candles. Ricketts' (1907) conclusion that the virus of spotted fever is held back by Berkefeld filters is confirmed by Spencer and Parker (1924, *c*), and by Spencer (1925). The American Trench Fever Commission (Strong, 1918) found that the virus of trench fever under 760 mm. of mercury would pass through a Chamberland L filter, which held back *B. typhosus* before and after the experiment (Swift, 1920). Theiler believes that the virus of heartwater will not pass through Berkefeld and Chamberland filters; but Knuth and du Toit (1921) class it among the filtrable viruses.

DISTINCTION BETWEEN RICKETTSIA AND CELL GRANULES

With these characteristics in mind, it is difficult, at first sight, to understand how some of the earlier workers in this field could seriously have questioned the conclusion that rickettsiae are, in fact, true and independent micro-organisms (Woodcock, 1925, is still unconviced of the organismal nature of several of them). The pioneer investigators were, however, concerned primarily with a single species, *R. prowazeki*, which is the most difficult of all to observe in sections of human and mammalian tissues. Not only is it present in very small numbers, so that it often requires days of search to discover typical examples, but its properties are obscured by the accompanying vascular lesions, with the result that workers who have not themselves seen how distinctive are these rickettsiae in well stained preparations may be pardoned for their incredulity, which was strengthened by the fact that all attempts at artificial cultivation proved negative. This is, however, not a sub-

ject that any longer demands space for presentation. The points to be borne in mind in making a distinction between rickettsiae and granules of different kinds, given by Wolbach and his colleagues, by Cowdry (1923, *b*), and by Nicholson (1923), should be sufficient.

CRITERIA FOR THE IDENTIFICATION OF RICKETTSIAE

In their survey of the distribution of rickettsiae in insects, Hertig and Wolbach (1924) have used as a working basis Cowdry's (1923, *b*) definition—"namely, gram-negative, intracellular, bacterium-like organisms, found in arthropods—recognizing as he points out that at least some of such organisms are probably merely bacteria." They propose, in the future, the restriction of "the term 'Rickettsia' to proved pathogenic micro-organisms, having the following characteristics: small size, pleomorphism, slight affinity for anilin dyes, and intracellular habitat."

This is probably the best definition that has been offered, and no one will deny the need for greater conservatism in the use of the word "rickettsia." The wisdom, however, of including only proved pathogenic micro-organisms under this designation is doubtful. This action would reduce our list of rickettsiae to three, including only two, *Dermacentroxenus rickettsi* and *R. ruminantium,* in addition to the type species; because we do not know positively whether the rickettsiae associated with trench fever and tsutugamuchi disease constitute the actual etiologic agents. Neither do I think that we should insist too strongly on the presence of pleomorphism.

In practice the definition may be slightly recast to advantage as follows: Gram-negative, bacterium-like organisms of small size, usually less than half a micron in diameter, which are found intracellularly in arthropods, which may be more or less pleomorphic and stain rather lightly with analin dyes, but which resemble in most of their properties the type species, *R. prowazeki.*

COMPARISON OF RICKETTSIAE WITH THE "SYMBIONTS" OF ARTHROPODS

Although the term "symbiont" denotes a very close degree of adaptation between a micro-organism and its host, which is fulfilled by some rickettsiae, it is usually applied to certain mold and bacterium-like micro-organisms which differ sharply from the more typical rickettsiae. As examples may be cited the "bacteroids" of cockroaches, the symbionts of tsetse flies, first observed by Koch, the symbionts of ticks (Cowdry, 1925, *b*), and many similar organisms (Buchner, 1921; Nuttall, 1923).

These symbionts, which may be algae, fungi or bacteria, are larger than most rickettsiae, are not so frequently disposed in pairs, and are far more easily demonstrated in microscopic preparations. When

TABLE 1.—*Distribution of Rickettsia in Arthropods*

Class	Order	Family	Genus and Species	Observed
Arachnida	Araneida.....	Attidae.....	Salticus scenicus (jumping-spider)	Cowdry (1923 b)
Arachnida	Acarina.....	Trombidiidae....	Lucoppia curviseta (mite) Atomus sp. (mite)	Cowdry (1923 b)
Arachnida	Acarina.....	Argasidae.....	Ornithodorus moubata (tick)	Hertig and Wolbach (1924)
Arachnida	Acarina.....	Ixodidae.....	**Amblyomma hebraeum** (Heartwater tick)	Cowdry (1925 d)
Arachnida	Acarina.....	Ixodidae.....	**Dermacentor venustus** (Rocky Mountain spotted fever tick)	Ricketts (1909), Wolbach (1917)
Arachnida	Acarina.....	Ixodidae.....	Dermacentor variabilis (dog tick)	Cowdry (1923 b)
Arachnida	Acarina.....	Gamasidae.....	Dermanyssus sp. (mite from doves)	Reichenow (1922)
Arachnida	Acarina.....	Gamasidae.....	Dermanyssus avium (bird mite)	Nöller (1920)
Hexapoda	Thysanura.....	Cinura.....	Lepisma saccharina (silver fish)	Cowdry (1923 b)
Hexapoda	Corrodentia...	Psocidae.....	Psocus sp. (dust louse).....	Sikora (1918, 1920)
Hexapoda	Corrodentia...	Atropidae.....	Dorypteryx pallida (book louse)	Hertig and Wolbach (1924)
Hexapoda	Mallophaga....	Trichodectidae...	Trichodectes pilosus (horse louse) R. trichodectae	Hindle (1921)
Hexapoda	Mallophaga....	Trichodectidae...	Trichodectes limax (goat louse)	Arkwright (1923)
Hexapoda	Mallophaga....	Philopteridae....	Lipeurus bacalus.....	Sikora (1922)
Hexapoda	Mallophaga....	Liotheidae.....	Trinoton sp.	Sikora (1922
Hexapoda	Mallophaga....	Liotheidae.....	Menopon pallidum (hen louse)	Sikora (1922), Hertig and Wolbach (1924)
Hexapoda	Hemiptera.....	Pediculidae.....	**Pediculus humanus**	
			(1) R. prowazeki.....	da Rocha-Lima (1916 a)
			(2) R. quintana (wolhynica)	Töpfer (1916),
			(3) R. pediculi.....	da Rocha-Lima
			(4) R. rocha-Limae.....	Weigl (1921, 1924 a,b)
			(5) R. (Cairo).....	Arkwright and Bacot (1923 b)
Hexapoda	Hemiptera.....	Pediculidae.....	Linognathus stenopsis (goat louse) R. linognathi	Hindle (1921)
Hexapoda	Hemiptera.....	Pediculidae.....	Phthirius pubis (pubic louse)	Guimarais (1922), de Mello and associates (1923)
Hexapoda	Hemiptera.....	Acanthiidae.....	Cimex lectularius (bedbug) R. lectularia	Arkwright, Atkin, and Bacot (1921)
Hexapoda	Neuroptera....	Chrysopidae.....	Chrysopa oculata (lace-winged fly)	Cowdry (1923 b)
Hexapoda	Diptera.....	Culicidae.....	(1) Culex pipiens (mosquito)	Nöller, Sikora (1920)
			(2) Culex pipiens.....	Hertig and Wolbach (1924)
Hexapoda	Diptera.....	Chironomidae...	Culicoides sanguisuga (sand fly)	Hertig and Wolbach (1924)
Hexapoda	Diptera.....	Tabanidae.....	Tabanus pumilis (horse fly)	Hertig and Wolbach (1924)
Hexapoda	Diptera.....	Tabanidae.....	Tabanus costalis (greenhead)	Hertig and Wolbach (1924)
Hexapoda	Diptera.....	Hippoboscidae...	Melophagus ovinus (sheep-ked) R. melophagi	Nöller (1917 a, b), Jungmann (1918), Arkwright (1921), Thiel (1925)
Hexapoda	Diptera.....	Cicadidae.....	Tibicen septendecim (seventeen year "locust")	Cowdry (1925 a)
Hexapoda	Siphonaptera..	Pulicidae.....	Ctenophalus felis (cat-flea) R. ctenophali	Sikora (1918, 1920)
Hexapoda	Siphonaptera..	Pulicidae.....	Ctenophalus canis (dog-flea)	Cowdry (1923 b)
Hexapoda	Siphonaptera..	Pulicidae.....	Pulex irritans (human flea)	Cowdry (1923 b)
Hexapoda	Coleoptera.....	Ptinidae.....	Sitodrepa panicea (drug-store beetle)	Hertig and Wolbach (1924)
Hexapoda	Hymenoptera..	Ichneumonidae..	Casinaria infesta (ichneumon-fly)	Cowdry (1923 b)

present, they always occur, to the best of our knowledge, in all members of the species infested. On the other hand, all pathogenic rickettsiae and several other rickettsiae which are presumably nonpathogenic, are only occasional visitants in their arthropod hosts. *R. prowazeki*, by unrestricted multiplication in the intestinal lumina of lice, often kills them—a phenomenon never observed in the case of the symbionts. Many of the symbionts and the rickettsiae which most closely approximate to them in their properties are cultivatable on artificial mediums, while the true rickettsiae, which are divergent from the symbionts in their characteristics, are extremely difficult or impossible to cultivate by our present methods of technic. There is still another distinction, namely, that in their location the symbionts are usually restricted to certain cells, which, through hypertrophy and other modifications, are specially adapted to contain them and comprise the so-called "mycetomes." Occasionally rickettsiae may be similarly housed in mycetomes, as, for instance, *R. lectularia* of the bedbug; but even in this insect they possess a marked ability to invade other tissues not exhibited by any "symbionts."

THE DISTRIBUTION OF RICKETTSIAE IN ARTHROPODS

Very little information is available on this aspect of the rickettsia problem. Thus far, forty-four organisms styled "rickettsiae" have been reported; but the majority of these have been studied only superficially. The hosts of the nonpathogenic forms include, according to Wolbach (1925), "fourteen species of arachnids, ticks, mites, and spiders, and twenty-two species of hexapods (insecta) distributed in nine orders, including numerous non-blood-sucking insects, as well as lice, ticks and midges." Rickettsiae have never been reported in the third great class of arthropods, called *Crustacea*. In some unpublished studies, Cowdry examined about ten individuals of each of thirty-four species of crustaceans, comprising, for the most part, marine forms collected at Woods Hole, with uniformly negative results.

In table 1 the different species are listed in which rickettsiae have been found. It will be noted that several of the larger forms of rickettsiae described in ticks have been omitted (Cowdry, 1925 *b*), because they conform more closely to the "symbionts" mentioned above. The forms that contain rickettsiae which are probably pathogenic are given in capitals. These are found only in lice and ticks. If it is finally shown that tsutsugamuchi disease is caused by a rickettsia, the mite *Trombicula akamuchi* will have to be included.

It is impossible to arrive at any definite figures of the percentage of the different species of arthropods infested with rickettsiae, because so many observers have failed to record systematically the species that were examined in vain for rickettsiae. Moreover, it will be readily

TABLE 2.—*Pathogenic Rickettsiae in Mammalian Tissues*

	Typhus R. prowazeki	Spotted Fever Dermacentroxenus rickettsi	Trench Fever R. quintana	Tsutsugamuchi Disease R. nipponica ?	Heartwater R. ruminantium
Morphology.....	(a) Ovoid, somewhat lanceolate bodies in pairs, 0.2-0.3 × 1 microns; (b) smaller, coccoid bodies (Wolbach, Todd and Palfrey, 1922)	(a) Paired, 0.2-0.3 × 1 microns; (b) rods, 1 micron, often with polar granules; (c) rounded forms (Wolbach, 1923)	Unknown.....	Cocci 0.3-0.4 microns, diplococci 1 micron in length, and bacilli 1.5 microns in length (Nagayo and associates, 1924)	Uniform coccoid bodies, 0.2-0.4 microns, rarely in pairs
Microchemical reactions	Best seen after Zenker fixation and Giemsa staining; larger paired bodies stain more readily than cocci and are surrounded by slight halo (Wolbach, Todd and Palfrey, 1922), gram-negative and not acid resistant	The same, but more readily visible	Unknown	Best stained by azur II after Zenker fixation (Nagayo et al., 1924)	The same, but more easily detected than any other pathogenic rickettsia; may even be colored by hematoxylin and eosin and by iron hematoxylin
Position.....	Usually in endothelial cells (Wolbach, Todd and Palfrey, 1922)	In endothelial cells and smooth muscle of media (Wolbach, Todd and Palfrey, 1922); in endothelial cells which collect around the adventitia (Wolbach, 1923); in vascular lumina, giant cells, liver cells, and mononuclear leukocytes (Nicholson, 1923); in blood stream (Ricketts, confirmed by Wolbach, 1923)	In peripheral blood (Jungmann, 1916; Töpfer, 1916, and Kuczinski, 1917); existence, however, not generally accepted	In histiocytes, reticuloendothelial cells and polymorphonuclear leukocytes (Nagayo et al., 1924)	Restricted to endothelial cells which rupture and discharge into the blood stream
Arrangement.....	"Globular massing of organisms is the most characteristic appearance of Rickettsiae in human lesions" (Wolbach, Todd and Palfrey, 1922)	Single and in clumps.....	Unknown.....	.....	Greater tendency to spherical clumping than any other rickettsia
Distribution.....	Extensive but with marked tendency to localize in skin (Wolbach, Todd and Palfrey, 1922)	Very extensive	Unknown.....	Extensive (skin, lymph glands, spleen, liver and lungs) (Nagayo et al., 1924)	Very extensive without concentration in skin
Association with febrile reaction	Usually before thirteenth day of disease (Wolbach, Todd and Palfrey, 1922)	Increase progressively from first to fifth or last day of fever (Nicholson, 1923)	Unknown.....	.....	Occur chiefly in six day period after temperature has commenced to decline
Association with lesions	Accompanied by severe vascular lesions (Wolbach, Todd and Palfrey, 1922)	Accompanied by similar but less extensive lesions (Wolbach, 1923; Nicholson, 1923)	Unknown.....	Accompanied by vascular lesions (Nagayo et al., 1924)	Accompanied only by great swelling of the endothelial cells without other signs of injury

understood that the number found in any special group will usually be less than the actual number present, since the possibility is always to be considered that if a larger number of individuals of each species had been examined, it is quite likely that rickettsiae would have been discovered in species reported negative on insufficient grounds. Similarly, if individuals had been taken at regular intervals throughout the year, in more localities and in a wider range of physiologic conditions, or had been examined more closely in better sections, rickettsiae might well prove to be of more general occurrence than is generally supposed.

While the majority of species which possess rickettsiae live entirely on mammalian blood (*Pediculus humanus, Amblyomma hebraeum*, etc.), one is insectivorous (*Salticus scenicus*), two are insectivorous in larval stages, becoming vegetarian in adult life (*Casinaria infesta* and *Chrysopa oculata*), one is chiefly vegetarian, but will eat wool (*Lepisma saccharina*), and two are wholly vegetarian (*Atomus sp.* and *Lucoppia curviseta*). In view of these facts, we can hardly go further than to say that although blood feeding may determine the presence of some rickettsiae, it is certainly not responsible for the occurrence of all of them. Neither is it possible to link the presence of rickettsiae with some recurring phase in the physiologic behavior of the several species containing them. Many are mammalian ectoparasites, but others are free-moving and winged. It is true that rickettsiae have not been described in aquatic insects, but there is no record that such forms have been sufficiently studied to justify any generalization regarding them.

Enough has been said to show that it is exceptional for rickettsiae (using this term in a broad sense) to be associated with disease. The influence, if any, of changes in season, of variations in moisture, of temperature, of illumination and other possible factors on the distribution of rickettsiae have not, as yet, been considered.

When we remember that in all some two or at most three hundred species have been examined for rickettsiae, and that rather hastily, in comparison with the two or three hundred thousand existing species of arthropods, it is evident that many of these organisms, both pathogenic and nonpathogenic, remain, in all probability, to be discovered. In other words, the limitations of the group are, at present, wholly unknown.

CLASSIFICATION OF RICKETTSIAE

Wolbach (1925) has amplified an earlier and helpful preliminary classification of rickettsiae (Hertig and Wolbach, 1924), in which they are divided into three main groups.

(*a*) Micro-organisms, the dominant phase of which is an extracellular one in the lumen of the host.

Under this heading he includes *R. pediculi* (i. e., *R. quintana* and *R. wolhynica*), *R. melophagi*, and other less known organisms, occurring chiefly in different kinds of lice. "These extracellular rickettsiae can probably all be cultivated on artificial culture mediums. They stain more readily than the intracellular rickettsiae, and under the dark-field they are more refractive than the intracellular rickettsiae. On the whole, there is very little, if any, reason for regarding them as different from familiar bacteria. The main reason for retaining them in this group is their perfect adaptation to their insect hosts, including the mechanism of hereditary transmission."

(*b*) Intracellular micro-organisms, having a uniform morphology, coccoid and diplococcoid.

In this subdivision he places the rickettsiae of the book louse (*Dorypteryx*) and of the sand fly (*Culicoides*). These rickettsiae are nonpathogenic, "may be distributed in the cells of various organs, and seem to be invariably present in the ovaries, which accounts for their hereditary transmission. . ." Although perfectly adapted to their hosts, they have not given rise to specialized cells to house them (mycetomes).

(*c*) Intracellular pleomorphic micro-organisms, exhibiting coccoid, rod and filamentous forms.

This group includes the rickettsiae of typhus and Rocky Mountain spotted fever, as well as those inhabiting the bedbug and the mosquito (*Culex pipiens*). These differ markedly in their distribution in the various tissues and in the effects on their hosts. It is probable that *R. ruminantium* of heartwater should be placed in this category and perhaps *R. nipponica* as well, if the investigations of Sellards (1923) and of Nagayo and his associates (1924) are confirmed.

PATHOGENICITY OF RICKETTSIAE AND RESERVOIR OF INFECTION

Evidently, the degree of adaptation of rickettsiae to their hosts varies within wide limits. There is, indeed, a gradation between a condition of true symbiosis on the one hand and of parasitism on the other; but the tendency of the majority is toward symbiosis. According to Hertig and Wolbach (1924), the pathogenicity of the rickettsiae associated with typhus fever, spotted fever and trench fever in man "would seem to be either an accidental or an acquired characteristic, so far as the group is concerned. In this connection, however, it may be noted that while the rickettsiae typically inhabit arthropod tissues, an arthropod reservior of the parasites is unknown in typhus and trench fever, while in Rocky Mountain spotted fever, although the infection may persist for generations in the tick, it is by no means certain that the parasite can be indefinitely maintained in ticks."

The best example of a rickettsia which must possess some reservoir other than that supplied by its transient arthropod host is *R. ruminantium,* the etiologic agent of heartwater. With each brood of ticks this organism is definitely eliminated, because it does not pass from one generation to another through the eggs. Unless some reservoir of rickettsiae is at hand, this species could not survive. The case is somewhat different from that of trench fever, because it is known that lice may pick up *R. quintana* when fed on persons several months after recovery, whereas in heartwater the blood usually loses its infectivity, when tested, by direct inoculation and tick transmission to susceptible animals, very soon after the return of the temperature to normal in surviving animals. For this reason, sheep, goats and cattle which have recovered from heartwater are less likely to constitute rickettsiae reservoirs.

R. prowazeki of typhus fever is not only eliminated in this way with each successive generation, but is, in addition, definitely pathogenic for lice, so that it assists in the extermination of its vectors.

Unless other mammalian reservoirs exist for these rickettsiae, and no such reservoirs are known, the perpetuation of these species (*R. prowazeki, pediculi* and *ruminantium*) would seem to be conditioned by the presence of the specific vectors in localities where the diseases are constantly occurring, or where the interval between successive cases of the disease is not longer than the maximum time required for the vectors to pass through one generation.

In addition to the transient nature of their sojourn within the vectors, all these pathogenic rickettsiae are restricted to the alimentary tracts of their invertebrate hosts, with the single exception of *Dermacentroxenus rickettsi,* which may invade many other organs, including the salivary glands. According to Brumpt (1918), *R. prowazeki* may likewise occur in the salivary glands, but Arkwright and Bacot (1923, *b*) emphasize its absence in this location. That the pathogenic rickettsiae are primarily inhabitants of the gut, is interesting and may be distinctive. Hindle and Duncan (1925) mention the absence of bacteria in the alimentary canal of ticks and describe experiments which seem to prove that the contents of the stomach of *Argas persicus* contain lytic and inhibitory principles for several kinds of bacteria, and *Argas persicus* is merely one of many blood-feeding arthropods in the intestines of which bacteria are conspicuous by their rarity. Experimentation along these lines may bring to light important physiologic differences between rickettsiae and bacteria, because the former seem to thrive under conditions which almost completely inhibit the latter.

That pathogenicity is not wholly and invariably conditioned by entry of the rickettsiae into the circulation of the vertebrate, on which their carrier is an ectoparasite, is shown by Nöller and Kuchling's

(1923) success in cultivating *R. melophagi* from the blood of sheep which showed no symptoms arising from its presence, and by Hertig and Wolbach's (1924) observation that feeding sheep-keds, containing rickettsiae, on their persons gave rise to no untoward results. In some unpublished experiments, Nicholson and Cowdry injected suspensions of the viscera of bedbugs, containing large numbers of *R. lectularia,* into mammals, birds, amphibians, and fishes by a variety of routes, including in rabbits even the intracerebral. The rickettsiae were also fed by mouth. In all cases they were enveloped and destroyed, or digested within a few hours. Never did they produce a generalized infection and seldom a marked local reaction. We do not know whether other rickettsiae, which are likewise classed as "nonpathogenic," are capable, under experimental conditions, of producing disease. Very few have been tried. Those that approximate most closely in their properties to the type species should be regarded with suspicion. Of these, the rickettsiae found in the human flea by Cowdry (1923, *b*) and in the mosquito and sand-fly by Hertig and Wolbach (1924) are of special interest.

THE STATUS OF DIFFERENT RICKETTSIAL SPECIES

As long as the study of rickettsiae continues to be chiefly concerned with a determination of their morphology and distribution, in default of suitable methods for their cultivation on artificial mediums, the question will remain whether organisms now grouped under a single species may not comprise physiologically distinct varieties, although morphologically they may be identical. For example, the symbiotic micro-organism, *B. radicicola,* which, like rickettsiae, has been confused with mitochondria, although it is in reality independent of them (Cowdry, 1923, *a*), has been resolved, through cultural methods, by Greig-Smith into three distinct races (Park and Williams, 1920).

This possibility that several different rickettsiae may be classed within a single species is more likely in the case of the nonpathogenic forms than in those which are associated etiologically with disease, because the production of a special disease is in itself a distinctive physiologic attribute which supplements distinctions made on the basis of morphologic and tinctorial properties. This applies chiefly to the rickettsiae actually present in the lesions, and much less directly to those in the vectors, because rickettsiae not causally related to disease are, with a single exception (*R. melophagi*), incapable of continued existence in vertebrates.

The systematic cultural experiments made by Noguchi (1926) with ticks which, microscopically, seemed to harbor only *Dermacentroxenus rickettsi,* have yielded surprising and instructive results. He was able to isolate three different rickettsia-like organisms which he has desig-

nated *B. rickettsiformis, B. pseudoxerosis* and *B. equedispersionis,* respectively. These are additional to and entirely distinct from the virus of spotted fever and from the typical bacteria (and symbionts ?) encountered by Wolbach. He states that they "are nonpathogenic for the guinea pig, rabbit and *Macacus rhesus* . . . all three are pleomorphic under certain cultural conditions, and the question arises whether or not the minute, non-pathogenic rickettsia forms and the somewhat coarser symbionts found in *Dermacentor venustus* are morphological variations, due to variations in nutrition, oxygen tension, tissue reactions, etc., in the different tissues and cells in which the organisms are embedded."

In other words, morphologic characteristics must be accepted with caution in the determination of species for the additional reason that they may only reflect environmental differences. Thus, forms of rickettsiae which look dissimilar may belong to one and the same species, just as surely as forms which appear identical may, in reality, be wholly distinct.

Perhaps nothing would be more effective in shedding light on the rickettsia problem than the systematic study by similar and additional cultural methods of the species identity of the rickettsiae occurring in lice (*Pediculus humanus*). On grounds that are chiefly morphologic, the existence of five species is often accepted (table 1), the bodies described by Töpfer (1917) in lice from cases of "war nephritis" being omitted on account of lack of evidence. The tendency, rightly, is toward conservatism in the recognition of species. Thus, the forms described as *R. quintana* and *R. pediculi* are considered identical, and Arkwright and Bacot (1923, *b*) suggest that the Cairo rickettsia "may be a non-virulent variant of *R. prowazeki.*" (The possibility that *R. prowazeki* is a mutant of *B. proteus* will be discussed subsequently.) This reduces the number of species in human lice from five to possibly three. Cultural methods, like those of Noguchi, might reveal the actual presence of a smaller or a larger number, probably of the latter.

There is also reason to believe that *Dermacentroxenus rickettsi,* as well as *R. prowazeki,* may, under certain conditions, lose its pathogenicity, in view of the discovery by Spencer and Parker (1923) that the virus of spotted fever passes through an avirulent, immunity-producing phase.

ETIOLOGIC RELATIONSHIPS OF RICKETTSIAE TO SPECIFIC DISEASES OF MAN AND MAMMALS

That the five diseases already alluded to are caused by the bites of arthropods which transmit the viruses may be considered fully established. What we have to examine is the evidence that in each case the virus is a specific rickettsia. For convenient reference, the properties

of the five supposedly pathogenic rickettsiae, so far as they are known, are summarized in tables 2 and 3. It will be seen that we have much information regarding the rickettsiae which are associated with typhus fever, Rocky Mountain spotted fever and heartwater, but that our knowledge of the other two is fragmentary.

Typhus Fever.—The evidence that *Rickettsia prowazeki* is the causative agent of typhus fever fulfils the postulates of Koch, if we regard the growth of rickettsiae in pure cultures, when introduced in vivo into the intestine of the louse, as equivalent to their growth in artificial medium in vitro.

(*a*) Constant Occurrence of *R. prowazeki* in Cases of Typhus Fever: This has been recognized chiefly as a result of the researches of Wolbach and Todd (1920), Stevenson and Balfour (1921), and Wolbach, Todd and Palfrey (1922). In consideration of the data given in the foregoing paragraphs and the instructions supplied by the last named investigators, the identification of *R. prowazeki* in tissues can no longer be regarded as questionable. There are, moreover, reasons to believe that rickettsiae of this species are present in the distinctive lesions of all cases of typhus fever.[3] For example, Wolbach, Todd and Palfrey found them "in the skin of twenty-five cases, which represents every case where the post mortem examination was made before the thirteenth day of the disease, and while the body was in a fresh condition." The criticism advanced that *R. prowazeki* is but one of several postmortem invaders is definitely disposed of by the observation made by these workers that "bodies indistinguishable from rickettsiae" were demonstrated in twenty-one out of twenty-eight pieces of skin excised antemortem. They also discovered *R. prowazeki* in the tissues of experimentally infected guinea-pigs.

Although rickettsiae has not thus far been regularly observed in the blood of typhus fever patients, their presence may be safely assumed for several reasons. It is in conformity with the fact emphasized by all the earlier workers, and now fully recognized, that rickettsiae are numerous in lice collected from typhus fever patients (Ricketts and Wilder, 1910; Hegler and von Prowazek, 1913; Sergent, Foley and Vialette, 1914, 1921, *a, b;* da Rocha-Lima, 1916, *a, b,* 1917; Nöller, 1916; Töpfer and Schüssler, 1916; Otto and Dietrich, 1917; Brumpt, 1918, and others).

3. My own failure to detect *R. prowazeki* in material from more than two out of twenty-four necropsies is to be explained on the supposition that the cases were not so carefully selected. Part of this material was given to me by Dr. Wolbach and part by Dr. Rajchmann. The rickettsiae which were observed conformed in every particular with those present in preparations made by Dr. Wolbach, which I enjoyed the privilege of examining.

Wolbach and his associates were the first to work with carefully pedigreed lice of two chief strains, one from the United States and the other reared by Bacot, at the Lister Institute. Continued observation of these lice over long periods of time proved that they were devoid of rickettsiae. When, however, they were fed on persons suffering from typhus fever, they acquired rickettsiae.[4] But still more convincing is the observation that when Atkin and Bacot (1922) permitted specimens of *Pedicinus longiceps* to feed on monkeys during attacks of typhus fever, these insects likewise acquired large numbers of rickettsiae. That this species of louse, belonging to a different genus and peculiar to monkeys, should normally harbor *R. prowazeki* is most improbable, because of the high degree of host-specificity shown by rickettsiae.

Conversely, in spite of diligent search, *R. prowazeki* has never been detected in the tissues or in the blood stream of patients or animals in conditions other than typhus fever

(*b*) Isolation of *R. prowazeki* in Pure Culture in the Alimentary Tract of Lice: In 1920, Weigl succeeded in obtaining a growth of *R. prowazeki* in the intestinal tract of normal lice by giving them intrarectal injections of leukocytes from typhus fever patients and from guinea-pigs infected with the disease.[5] His results were confirmed by Bacot and Segal (1920) who, using the same technic, secured similar growths of rickettsiae from a strain of typhus fever virus which had been maintained in guinea-pigs for more than a year. Still more recently, Arkwright and Bacot (1923, *a*, *b*) cultivated rickettsiae in the same way from typhus fever patients and typhus infected guinea-pigs.

Evidence pointing in the same direction has been obtained by Wolbach and Schlesinger (1923), who produced a growth of *R. prowazeki* within the cells of tissue cultures inoculated with a typhus fever virus which had been maintained in guinea-pigs for as long as three years. This achievement is significant because "it effectively disposes of the idea that *R. prowazeki* is an organism that accompanies the virus of typhus and is not itself the cause," for it is difficult to understand how otherwise it could have persisted in this manner in the guinea-pigs.

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4. The observation that rickettsia occur in lice fed on apparently healthy persons, which was made toward the close of the World War (Nicolle, Blanc and Conseil, 1914; Brumpt, 1918; Strong, 1919, *a*, *b*, and others) is, to some extent, deprived of significance by the supplementary information that persons who have suffered attacks of trench fever may remain virus reservoirs for as long as 443 days after the onset of the disease (Byam and Lloyd, 1919), which suggests the possibility that in some of these cases we are dealing with *R. quintana*.

5. The method has been improved by Bacot (1922), Schnabel (1923) and also by Sikora (1924). The virus is apparently closely associated with the platelets (Kusama, 1920; Segal, 1922; Arkwright and Bacot, 1923 *b*).

TABLE 3.—*Pathogenic Rickettsia in Arthropod Vectors*

	Typhus R. prowazeki	Spotted Fever Dermacentroxenus rickettsi	Trench Fever R. quintana	Tsutsugamuchi Disease	Heartwater R. ruminantium
Morphology	0.3 × 0.4 micron for single elements, 0.3 × 0.9 micron for double (da Rocha-Lima, 1916, a)	(a) Extranuclear bacillus-like form without chromatoid granules 0.5 × 1 micron, (b) very minute rods with chromatoid granules within nuclei, (c) larger lanceolate paired forms; less bacterium-like than any rickettsiae (Wolbach, 1923)	0.3 × 0.3-0.5 micron, round, oval, diplococcal or bacillary with stainable poles; shorter and thicker than the typhus organism (Töpfer, 1916); "more uniform in morphology, plumper and more definitely oval than R. prowazeki" (Wolbach, Todd and Palfrey, 1922)	Unknown....	Cocci, 0.2-0.3 micron; bacilli, 0.2-0.3 × 0.4-0.5 micron; diplococci, 0.2 × 0.8 micron; no filamentous forms
Microchemical reactions	Gram-negative; pale blue by Giemsa; multiplicative forms show also red staining substance; outlines less sharp than most bacteria; not acid-fast (Wolbach, Todd and Palfrey, 1922)	Gram-negative; pale blue by Giemsa, except chromatoid granules and larger paired forms which are purple; multiplicative form shows red staining substance in addition to the blue; not acid-fast (Wolbach, 1923)	Gram-negative; purple or red by Giemsa; "easier stained than R. prowazeki" (Wolbach, Todd and Palfrey, 1922); outlines less sharp than most bacteria; not acid-fast	Unknown....	Gram-negative; easily stained dark blue by Giemsa; outlines less sharp than most bacteria; multiplicative form as seen in smears exhibits also intermediate red staining material; not acid-fast
Position	Extracellular and intracellular	Extracellular, intracellular and intranuclear	Extracellular, but apparently sometimes intracellular (Sikora, 1921)	Unknown....	Chiefly intracellular, but sometimes extracellular
Arrangement	Haphazard in very large masses	Haphazard; singly, end to end or in clumps	In layers on surface of intestinal epithelium	Unknown....	Densely packed in characteristic, spherical, intracellular clumps
Distribution	In intestinal epithelial cells and in lumen; also occasionally in salivary glands (da Rocha-Lima, Brumpt, 1918)	In all tissues at certain phases of its life cycle, at other times more restricted (Wolbach, 1923)	In intestinal lumen, rarely within intestinal epithelial cells	Unknown....	In intestinal epithelial cells and in lumen
Effect on host	Not harmful	Eventually fatal	Not harmful	Unknown....	Not harmful
Infestation	Not hereditary	Hereditary (Ricketts)	Not hereditary (Arkwright, Bacot and Duncan, 1920)	Unknown....	No hereditary

Cowdry and Nicholson found that the nonpathogenic and easily recognizable *R. lectularia* will not survive more than two, or, at most, three hours in the tissues of these animals.

(*c*) Production of Typhus Fever with Cultures of *R. prowazeki:* These intrarectal cultures of *R. prowazeki,* and the tissue cultures containing the same organism, gave rise to typical attacks of typhus fever when inoculated into guinea-pigs. And, conversely, all attempts to produce typhus fever by the inoculation of material known to be devoid of *R. prowazeki* have failed.

Next to the association of *R. prowazeki* with typhus fever, the most characteristic property of the disease is the presence in the serum of agglutinins for *B. proteus* X 19 (Weil-Felix reaction). But it is universally recognized that *B. proteus* is not itself the cause of the disease (Breinl, 1924, *a*) for two reasons: first, because there is no evidence that it invades the tissues in cases of typhus fever (Wolbach, 1925), and second, because it is not constantly found in lice capable of transmitting the disease.

In order to reconcile the results of the histologic studies on *R. prowazeki* in infective lice with the data concerning the agglutinability of *B. proteus* X 19 by the serum of typhus fever patients, certain continental investigators have suggested the existence of a mutation. According to Friedberger, *R. prowezeki* is simply the form assumed in the louse by *B. proteus* X 19. This view is supported by Weigl (1923, 1924, *a*) and by Breinl (1924, *a, b. c*). The former includes under this single supposedly mutating species: (1) *R. prowazeki,* (2) *B. proteus* X 19 and (3) *B. typhi-exanthematici* of Plotz,[6] and Breinl adds to the list: (4) *Microbion typhi-exanthematici* of Barykin and Kritsch, and (5) certain micro-organisms isolated by Kuczinski. Agglutinins for *B. proteus* X 19 appear in guinea-pigs and rabbits after the injection of louse typhus virus (Breinl, 1924, *c*).

Breinl admits that typhus fever serums often agglutinate other organisms in addition to *B. proteus* X 19, but not in so high a dilution or so regularly and completely. This "polyagglutinability" is well known and widely admitted. According to Olitsky (1921): "The bacteria which, under the influence of the virus of typhus fever, thus invade the body of the guinea pig, are of several kinds, and vary not only among themselves, but also with the day of the fever on which the examination is made. Thus, on the first day of fever, Plotz's bacilli were recovered twice and anaerobic streptococci, *proteus* bacilli, aerobic diphtheroids, Gärtner type bacilli, and *Staphylococcus aureus* each once. On the second day, Plotz' bacilli were found four times, anaerobic streptococci three times, Gärtner type bacilli, aerobic diph-

6. Note, however, Olitsky's (1922, *a*) conclusion that this organism is not identical with the active agent of typhus virus.

theroids, *Bacillus welchii,* aerobic gram-positive diplobacilli, and *Staphylococcus aureus* each once. On the third day, Plotz bacilli were recovered once, as were anaerobic streptococci and Gärtner type bacilli. On the fourth day, *Staphylococcus aureus* was found twice and Plotz bacilli and *Bacillus proteus* each once." An equally rich bacterial flora is present in human cases, though it has not been so systematically studied.[7]

Positive Weil-Felix reactions have, moreover, been reported in cases of other diseases than typhus fever (Weil and Felix, 1916; Saequépée and Delavergue, 1919; Napier, 1919; and others). Of principal interest is a series of cases giving a positive Weil-Felix reaction, reported by Maxcy and Havens (1923) from the southern states, which they believe to be either mild typhus, or Brill's disease, although no insect vector was found, and the symptoms were not typical of typhus. Obviously, agglutinins for *B. proteus* X 19 are present in instances in which it is difficult or impossible to prove the action of *R. prowazeki,* although its occurrence has not been definitely excluded. Olitsky's (1925) demonstration that "*Bacillus proteus* X 2 and X 19, either in culture or in the brain of proteus infected guinea-pigs, is quite resistant to the action of glycerol, and differs markedly in this respect from the typhus virus" is also of importance in this connection.

According to Kuczynski, Brandt and Mashbitsch (1924), typhus fever is caused by *Proteus rickettsia-prowazeki* and may be defined as a specific acute proteus infection in man. Whether we accept *R. prowazeki* alone as the etiologic agent of typhus fever or as a mutant of *B. proteus* X 19 depends largely on the relative importance of the histologic demonstration of *R. prowazeki* in the tissues in cases of typhus fever by Wolbach and his associates, and of these recent serologic studies, which latter lie beyond the scope of this inquiry. Mention may, however, be made of Krukowski's (1923) discovery that the serum of typhus patients contains specific agglutinins for *R. prowazeki* and of Weigl's (1924, *a*) statement that the agglutination curve for *R. prowazeki* is identical with the X 19 agglutination and, further, that it is of a higher order than the Weil-Felix reaction. We shall await eagerly confirmation of Fejgin's (1924) experiments, which have been supported indirectly by Hauduroy (1925), that the inocula-

7. This is illustrated by numerous morphologic and cultural demonstrations of organisms in the blood of typhus fever patients or infected animals: Galesco and Slatineano (1906), Rabinowitch (1909, 1913, 1923), Ricketts and Wilder (1910), Gavino and Girard (1910), Hegler and von Prowazek (1913), von Prowazek (1915), Plotz, Olitsky and Baehr (1915), Borrel and his associates (1919), Kuczynski (1920), Sangiori (1921), de Sousa (1922), Otto (1922), Barykin and Kritsch (1923), de Mello and associates (1923). Yoshioka and Ando (1924), Kusama (1925), and others. Obviously, all of these accounts do not relate to R. prowazeki, although some of them may do so.

tion of guinea-pigs with the bacteriophage antiproteus produces a transmissible disease which confers immunity against subsequent inoculation with the virus of typhus fever, and, conversely, that experimentally induced typhus fever gives rise to a similar immunity against the antiproteus bacteriophage. Further information on the general serologic aspects of the problem is given by Breinl (1925, *a, b*), Hach (1925), Kuczynski and Brandt (1925), and others.

Rocky Mountain Spotted Fever.[8]—The evidence that *Dermacentroxenus rickettsi* is the causative agent of spotted fever is even stronger. It was summarized in 1919 by Wolbach as follows:

> 1. The constant occurrence of a micro-organism (*D. rickettsi*) of distinctive size and morphology in the lesions characteristic of the disease in man, monkey, rabbit and guinea-pig.
>
> 2. The constant presence of an identical micro-organism exhibiting undoubted evidences of developmental phases in ticks of proved infectivity, and the absence of similar forms in proved noninfective ticks.
>
> 3. The ability to recognize this specific micro-organism in the tissues and eggs of infective ticks in the presence of bacteria occasionally present in abundance in ticks of the species concerned.

To this has been added: the successful cultivation of the microorganism in virulent form in tissue plasma cultures (Wolbach, Pinkerton and Schlesinger, 1922; Wolbach and Schlesinger, 1923).

Making use of the criteria for the identification of *D. rickettsi,* advanced by Wolbach, this organism may be studied in infected mammals with a high degree of precision. Wolbach's observations have, in fact, been fully confirmed by Nicholson (1923), as far as mammalian tissues are concerned.

Experimentation with the virus in the arthropod vector is more difficult. Ricketts showed that both rickettsiae and virus are inherited from one generation to another in the eggs, which indicates how essential it is to prove the complete absence of all rickettsiae in larval ticks before any feeding experiments are commenced. Although it may be sufficient in the vast majority of cases to demonstrate that the bite of the female, from the eggs of which the larvae hatched, did not produce infection in a susceptible animal, it is conceivable that under certain conditions ticks possessing rickettsiae may fail to infect.

Another complication arises from the presence of a developmental cycle of the parasite in ticks. Wolbach has recognized three morphologic types:

> (1) An extra-nuclear bacillus-like form, without chromatoid granules, relatively large and only present in ticks during the initial multiplication of the para-

8. Rocky Mountain Spotted Fever—A Conference of Health Officials, Bull. Montana State Board of Health, Special No. 26, 1923; Parker (1918, 1919, 1921); Noguchi (1923); Connor (1924).

sites; (2) a relatively small, rod-shaped form with chromatoid granules, probably the same form seen within nuclei in sections of ticks, and rarely in smooth muscle cells in the blood vessels of mammals, and (3) a relatively large, lanceolate, paired form, present in ticks and in blood and lesions of mammals.

Cyclic alterations in the properties of the virus have been found by Spencer and Parker (1923, 1924, *a, b, c;* 1925), but unfortunately the alterations in the rickettsiae and in the virus have not been correlated. Of special interest is the discovery (already referred to) by these investigators of the occurrence of "a non-virulent, immunity-producing phase" of the virus in unfed ticks and the observation that this virus becomes reactivated to a virulent, infectious stage after the ticks ingest fresh blood.

Although rickettsia-like organisms, indistinguishable morphologically from *D. rickettsi* may occur in ticks which are incapable of transmitting Rocky Mountain spotted fever, they are culturally and immunologically distinct and apart from the virus (Noguchi, 1926). The evidence at hand fully justifies Wolbach's conclusion that *D. rickettsi* is, in fact, the causative agent of the disease.

Trench Fever.[9]—The evidence that *R. quintana* is the etiologic agent of trench fever is of a different character. Since trench fever is never fatal, it has not been possible to search systematically tissues obtained at necropsy for rickettsiae, as can be done in all the other diseases with which rickettsiae are associated. Thus, their presence or absence, in the lesions peculiar to the disease, remains unknown. In the peripheral blood of trench fever patients, Jungmann (1916), Töpfer (1916, *a, c*), and Jungmann and Kuczinski (1917) claim to have observed a few bipolar organisms resembling rickettsiae, but confirmation has not been forthcoming (Bruce, 1920). This inability to observe regularly *R. quintana* in the circulating blood is to be discounted as an argument against the pathogenicity of rickettsiae, because it has been found equally difficult or impossible to detect the rickettsiae of typhus, spotted fever and heartwater in the same location, in spite of the fact that the conditions are much more favorable for their demonstration. It seems, indeed, to be a general characteristic of the pathogenic rickettsiae that although they unquestionably do occur in the blood stream, they are never present abundantly or in sufficiently large and compact clumps to permit of microscopic study.

Another serious handicap in the study of the etiology of trench fever is the fact that, unlike the other diseases mentioned, it has not been possible, thus far, to transmit it to experimental animals; for the

9. For literature see official reports of American and British Trench Fever Commissions (Strong, 1918, and Bruce, 1920); Byam and his associates, Trench Fever (1919); Munk and da Rocha-Lima (1917).

claims advanced by Jungmann and Kuczinski (1917), Strisower (1918) and da Rocha-Lima that this can be done, have never been confirmed.

The virus has not been cultivated in vitro, nor in tissue cultures, nor have the methods of intrarectal injection into lice, advocated by Weigl, been applied.

There is strong reason, however, to believe that *R. quintana* is inseparable from the virus of trench fever, or identical with it, in consideration of the following observations made by Arkwright, Bacot and Duncan (1919, *b*).

(*a*) These investigators worked with pedigreed lice, reared on persons who had never suffered from trench fever. They found, in the first place, that the rickettsiae, like the virus, are not transmitted hereditarily from one generation to another in lice.

(*b*) The excreta and midgut contents of clean lice, fed on trench fever patients, become infective between five and twelve days after feeding, at which time, also, the rickettsiae appear (Mr. Bacot's own illness, described by him, 1921, is particularly convincing).

(*c*) In an infected box (of lice), not every louse appears to contain the virus of trench fever; neither does every louse contain Rickettsia in recognizable form or amount.

(*d*) A box, once infected, appears to remain so for two or three weeks, both as regards the virus of trench fever and the presence of Rickettsia. . . .

(*e*) The high infectivity of louse excreta is associated with the presence of enormous numbers of Rickettsia. . . .

(*f*) Lice or the excreta of lice, which have been proved to contain virus, as the result of successful inoculation, have, in most cases, when examined, been shown to contain large numbers of Rickettsia.

The only exception to this parallelism between the presence of rickettsiae and of the virus in the insect vectors is described in the Report of the British Trench Fever Commission. Lice which had fed on a trench fever patient were divided into two lots, one kept at 27 to 30 C. and the other at 17 C. The excreta of both proved infective, but rickettsiae were found only in lice maintained at 27 to 30 C. Obviously, the failure to detect rickettsiae cannot be considered as proof positive of their absence, since, in very small numbers, they may and probably often do escape observation by the most skilled observers.

As supplementary evidence, indicating the probability that *R. quintana* is the etiologic agent of trench fever, may be cited the unconfirmed observation of Ledingham (1920) that agglutinins for *R. quintana* are developed by rabbits inoculated with the excreta of lice infected with the virus of trench fever.

Tsutsugamuchi Disease.[10]—The status of *R. nipponica* as the suggested causative agent differs sharply from that of the other four pathogenic rickettsiae, chiefly for the reason that this organism has never been seen in the mites which transmit the disease, whereas all the other rickettsiae may easily be detected in large numbers in their arthropod vectors.

R. nipponica was first isolated by Sellards (1923) on a plate of "chocolate" blood agar. For subcultures he found Martin's agar, chocolated in a similar manner, very effective. In its morphologic and tinctorial properties it rather closely resembles *R. prowazeki.* During the course of transfer of the virus, he recovered this rickettsiae in pure culture four times, at fairly wide intervals, namely, "(1) from the spleen of a guinea pig in the sixth passage" in his laboratory; "from the spleens of guinea pigs (2) in the eighteenth and again (3) in the nineteenth passages, and also (4) from the heart blood of a monkey in the twenty-first passage . . . on inoculation of these cultures into guinea pigs, hemorrhagic lesions developed which were indistinguishable from the hemorrhages following the injection of the virus of tsutsugamuchi disease. The cultures were pathogenic, to some extent, for rhesus monkeys, the injected animals showing some evidence of active immunity against the virus." *R. nipponica* was not observed with certainty by Sellards in the tissues in association with the specific lesions.

Nagayo and his co-workers (1924) have, however, recently reported the discovery of "microcorpuscles" in the skin, lymph glands, spleen, liver and lungs of monkeys that received intradermal injections of the virus. These "microcorpuscles" possess, they believe, the characteristics of rickettsiae. They are colored best by azur II, after Zenker's fixation. The monococcal form measures about 0.3 to 0.4 micron, the diplococcal form 1 micron, and the bacillary 1.5 micron. They occur extracellularly and intracellularly in the histiocytes, reticulo-endothelial cells and rarely in polymorphonuclear leukocytes. No statement is made as to whether these organisms are related to *R. nipponica* of Sellards.

Heartwater.—As an object for experimental study, *R. ruminantium* possesses certain marked advantages over all known pathogenic rickettsiae. It may be more easily stained, occurs in the tissues of infected animals in larger numbers, and its presence is not obscured by destructive vascular lesions.

Since, however, it has not as yet been cultivated on artificial mediums, it can only be said, as in the case of some of the other rickettsiae, that it is inseparable from the virus of the disease. But this

10. For literature see: Kawamura and Yamaguchi (1921), and Ishiwara and Ogata (1924).

is, after all, as much as may be said of any pathogenic micro-organism, cultivatable or noncultivatable. The evidence that *R. ruminantium* is the etiologic agent of heartwater may be summarized:

(*a*) *R. ruminantium* occurs in cases of heartwater, in the endothelial cells of the smaller blood vessels in three species (sheep, goats, and cattle) and is uniformly absent in control, healthy animals and in animals suffering from other diseases.

(*b*) The duration of residence of *R. ruminantium* in the tissues of animals during an attack of heartwater corresponds to the period of infectivity of the blood when inoculated into other susceptible animals.

(*c*) Since neither the virus (Lounsbury) nor the rickettsiae is transmitted hereditarily in the tick from one generation to another through the eggs, newly hatched larvae are free from both virus and rickettsiae.

(*d*) When newly hatched larvae are fed on cases of heartwater, at a time when rickettsiae may be demonstrated microscopically in the tissues, they acquire rickettsiae, whereas control larvae fed on normal animals do not.

(*e*) If these larvae are allowed to molt, the resulting nymphae, which had fed as larvae on cases of heartwater, and which contain rickettsiae, are capable of producing attacks of heartwater when fed on susceptible hosts. The control nymphae, which had fed as larvae on normal animals, are, on the contrary, unable to cause heartwater.

(*f*) When the tissues of animals which have thus been infetced with heartwater are examined microscopically, rickettsiae identical with those originally seen in the sick animals, and encountered again in the infective ticks, are readily observed.

It has also been proved that the rickettsiae, like the virus, pass through the second molting period (i. e., from nymph to adult), and may then be recognized histologically. Wherever the virus is, except in the circulating blood of mammals, the rickettsiae may be clearly distinguished.

DISEASES UNDER SUSPICION OF BEING CAUSED BY RICKETTSIAE

Since almost all of our knowledge of these pathogenic rickettsiae has been contributed within the short space of a single decade, it is reasonable to suppose that further investigation will bring other diseases under this category.

On the basis of our present data regarding the more or less well-known rickettsiae, the suspicion that others operate in diseases of unknown etiology may be entertained in acute, febrile conditions which: (1) are transmitted by blood-feeding arthropods; (2) confer in the survivors a more or less lasting immunity; (3) exhibit a positive Weil-

Felix reaction; (4) involve lesions of the blood vessels frequently with exanthem, and (5) are caused by viruses which are nonfiltrable or filtrable with difficulty.

It is obviously not to be expected that all of these clues will be offered in a single case. Fevers that are particularly interesting from the point of view of their possible causation by rickettsiae are: (*a*) Brill's disease; (*b*) tick typhus and many conditions that may be allied to it (Megaw, 1925); (*c*) a series of cases giving a positive Weil-Felix reaction, occurring in the southern states (Maxcy and Havens, 1923, and Sinclair and Maxcy, 1925); and (*d*) pseudotyphus in the Dutch East Indies, possibly allied to tsutsugamuchi disease (Walch and Keukenschrijver, 1925).

Töpfer's (1917) idea that rickettsiae may be concerned in the etiology of "war nephritis" has not been substantiated. Sikora (1924, *a*) has found rickettsia-like bodies in a peculiar disease of cats of unknown causation.

But rickettsial agents of disease are not necessarily limited to vertebrates. The newly recognized group of extremely minute organisms, which are said to be parasitic within the nuclei of certain insects, in which they produce a highly contagious disease (Paillot, 1926), is of special interest. The intranuclear position of these parasites calls to mind the intranuclear phase of the rickettsia of Rocky Mountain spotted fever, as described by Wolbach. Like rickettsiae, these tiny organisms were first considered by von Prowazek to be allied to the *Chlamydozoa*—a conclusion, however, which Paillot's most recent work does not support. He believes them to occupy an intermediate position between bacteria and *Protozoa*. It is remotely possible, also, that certain diseases of plants may be produced by rickettsiae. The peculiar, gram-negative organisms, described by Sorokin (1926) in tomato mosaic, are of great importance in this connection, although they are somewhat larger than the pathogenic rickettsiae, while the parasites of Paillot are smaller. The mosaic virus is insect-transmitted, and in this respect resembles rickettsiae.

SUMMARY

There is strong evidence that typhus fever, Rocky Mountain spotted fever, and heartwater are caused by rickettsiae. It is highly probable that *R. quintana* is the etiologic agent of trench fever. The relation of *R. nipponica* and of the "microcorpuscles" of Nagayo to tsutsugamuchi disease remains very ill defined, but there are many points concerning the virus, its mode of transmission and the distinctive lesions of the disease which indicate the likelihood that it is produced by some form of rickettsia.

It is conceivable that the properties of these pathogenic rickettsiae may be subject to variation, several strains existing, as is the case with

some bacteria. For example, it is known that the virus of Rocky Mountain spotted fever passes through an immunity-producing, avirulent phase, and it has been claimed that *R. prowazeki* is a mutant of *Bacillus proteus.*

In addition to the disease-producing rickettsiae, thirty or forty species of nonpathogenic rickettsiae are recognized, depending on the criteria used in their determination. Those that correspond most closely to the pathogenic forms are found in the human flea, in the sand-fly and in the mosquito. The balance between symbiosis and parasitism is, moreover, a delicate one, which may be upset by factors largely unknown.

Since investigations extending over a period as short as ten years have revealed such a definite and far-reaching relation between rickettsiae and disease, we may reasonably expect that within another decade our knowledge along these lines will be considerably augmented. At present we seem to be in a state of transition from an approach which is predominately cytologic to cultural and serologic methods of study. The cytologic element consists chiefly of the identification within the distinctive lesions of uncultivatable organisms which are so tiny, which stain so faintly, and which are present in such small numbers, even under the most favorable conditions, as to make their discovery difficult.

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News and Notes

Death of Australian Pathologist.—Sir Harry Brookes Allen, professor of pathology and dean of the faculty of medicine, Melbourne University, formerly editor of the *Australian Medical Journal,* has died at the age of 71.

Appointments at University of Pennsylvania.—In the school of medicine, David H. Bergey has been promoted to professor of hygiene and bacteriology; Morton McCutcheon, to assistant professor of pathology.

Dr. Hartman Appointed Acting Dean.—Dr. Henry C. Hartman, professor of pathology at the University of Texas, has been appointed as acting dean of the medical school, to succeed Dr. William Keiller, professor of anatomy since 1891, who has resigned.

Dr. Lewis Guggenheim Fellow.—Dr. Julian H. Lewis, assistant professor of pathology at the University of Chicago and associate member of the Sprague Institute, has been awarded a Guggenheim fellowship and will go to Europe to study problems in immunity.

In Honor of Eberth's Ninetieth Birthday.—*Beiträge zur pathologischen Anatomie und zur allgemeinen Pathologie,* familiarly known as *Ziegler's Beiträge,* volume 74, no. 1, is dedicated by the Pathological Institute at Halle a.L. to Carl Josef Eberth, the discoverer of the typhoid bacillus, in commemoration of his ninetieth birthday. The frontispiece is a striking photograph of Professor Eberth, who retired from academic work about fourteen years ago.

Osler Memorial Volume.—This book of 630 pages, which has just been issued under the auspices of the International Association of Medical Museums, contains memorial articles, a classified and annotated bibliography of Osler's writings, a bibliography about Osler, and more than one hundred fine illustrations. The book is privately issued, but may be obtained for $10 a copy from Dr. Maude E. Abbott, McGill University, Montreal, Canada.

Medical Fellowships of National Research Council.—Applications for fellowships in medicine of the National Research Council, in order to receive consideration at the September meeting of the medical fellowship board, should be filed on or before August 1. Communications should be addressed to the chairman of the Medical Fellowship Board, National Research Council, Washington, D. C.

Stanley P. Black Memorials.—Physicians in Pasadena are endeavoring to provide for a Black Fund for lectures. The Black Memorial Hall in the Professional Building, Pasadena, was completed, March 1, and Dr. Aldred S. Warthin was the first lecturer. The committee requests the support and interest of physicians in this project; checks may be mailed to the secretary, Dr. Leroy B. Sherry, 65 North Madison Avenue, Pasadena. Dr. Stanley P. Black was a pioneer in scientific medicine, particularly pathology, in Los Angeles and Pasadena, and was held in the highest esteem by the medical profession there and elsewhere. In Los Angeles a Black Memorial fund of about $5000.00 has been collected under the auspices of the Clinical and Pathological Society.

GRANTS MADE IN 1926 BY THE COMMITTEE ON SCIENTIFIC RESEARCH OF THE AMERICAN MEDICAL ASSOCIATION

Grant 83: Roy L. Moodie, professor of anatomy in the college of medicine in the University of Illinois, $65 for excess cost of illustrations of article on paleopathology.

Grant 84: Harry L. Huber, clinical associate in medicine in the University of Chicago, $1,200 for continuation of work on the chemical and immunologic properties of the pollens concerned in hay-fever and allied conditions.

Grant 85: Barnett Sure, professor of chemistry in the college of agriculture of the University of Arkansas, $300 for study of a dietary factor concerned in the secretion of milk.

Grant 86: P. E. Lineback, professor of anatomy, Emory University, Georgia, $250 for a study of the macula lutea and fovea centralis with the object of establishing, if possible, a clearer morphologic foundation for binocular vision.

Grant 87: A. W. Meyer, professor of anatomy in Stanford University, $1,200 for continuation of work on the tissue changes in experimental scurvy.

Grant 88: Emery R. Hayhurst, professor of hygiene and head of the department of public health in the University of Ohio, $1,000 toward the expenses of an investigation of pulmonary silicosis, largely by means of radiography, among grindstone and cutstone workers in northern Ohio.

Grant 89: Emery R. Hayhurst, professor of hygiene; Charles B. Morrey, professor of bacteriology, and Dana J. DeMorest, professor of metallurgy, University of Ohio, $500 for expenses of an experimental study of the effect of breathing combustion products of carbonaceous fuels on the susceptibility to pneumonia.

Grant 90: Carl W. Apfelbach, instructor in pathology in Rush Medical College (University of Chicago) and resident physician in the Presbyterian Hospital, and Edwin M. Miller, assistant clinical professor of surgery in Rush Medical College, $500 toward the expenses of a study of the effects of the destruction of glomeruli in the kidney of the dog.

Grant 91: Samuel A. Matthews, professor and head of department of physiology, pharmacology and therapeutics in the school of medicine of Loyola University, Chicago, $150 for materials for the study of the antagonistic action between magnesium salts and the parathyroid hormone.

Grant 92: H. W. Manwaring, professor of bacteriology and experimental pathology in Stanford University, $750 for expenses of investigation of fundamental problems of anaphylaxis and immunity.

Grant 93: Victor C. Jacobson, professor of pathology, Albany Medical College, $1,200 for further experimental study of endometriosis and allied problems.

Grant 94: Robert L. Benson, professor of pathology in the school of medicine in the University of Oregon, $800 toward the expenses of an experimental study of arteriosclerosis.

Grant 95: Nicholas W. Popoff, volunteer worker under Prof. A. A. Maximow in the department of anatomy in the University of Chicago, $240 for work on the histogenesis of the thymus in vitro.

Grant 96: Aldred Scott Warthin, professor of pathology, and George R. LaRue, associate professor of zoology and director of the biologic station, University of Michigan, $2,000 for an investigation of *Dibothriocephalus latus* infection, particularly in Michigan.

Abstracts from Current Literature

Pathologic Physiology

GLYCOLYSIS AT VARYING BLOOD-SUGAR LEVELS. I. I. LEMANN and R. T. LILES, J. Lab. & Clin. Med. **11**:339, 1926.

Glycolysis proceeds at a lessened rate when the level of blood sugar is raised, not only by glucose (or other food) ingestion, but also by intravenous glucose infusion.

The characteristic behavior of glycolysis in diabetic blood specimens may be related to the quantitative level of the blood sugar rather than to any essential quality of the blood.

Administration of insulin does not affect the characteristic behavior of glycolysis either in diabetic or in nondiabetic blood.

No important rôle is to be attributed to oxalate in evaluating the inhibition of glycolysis.

AUTHORS' SUMMARY.

NOTES ON BASAL METABOLISM. VIII. TABLES OF VALUES OF THE DU BOIS SURFACE AREA FORMULA. WILLIAM H. STONER, J. Lab. & Clin. Med. **11**:355, 1926.

Values of the Du Bois formula for human surface area are tabulated by unit centimeter and kilogram intervals for individuals of 110 to 200 cm. in height and of 20 to 110 Kg. in weight.

AUTHOR'S SUMMARY.

NON-PARASITIC CHYLURIA. A. A. KUTZMANN, Ann. Surg. **82**:765, 1925.

This article is important for its review of the literature and bibliography on the subject. The condition has been found in a variety of diseases such as diabetes, pernicious anemia, tuberculosis of the peritoneum and malignancy. The etiology is obscure, most plausible being the theory of lymphatic block and abnormal communication with the urinary tract. The author reports a case of chyluria from the left kidney, in which was found a perinephric abscess due to *B. coli* infection and a communicating sinus to the kidney. Nephrectomy was performed, with resulting cessation of the chyluria, for which no cause could be determined.

N. ENZER.

THE INFLUENCE OF ORALLY ADMINISTERED CALCIUM SALTS ON THE SERUM CALCIUM OF NORMAL AND THYREOPARATHYROPRIVIC DOGS. A. M. HJORT, J. Biol. Chem. **65**:783, 1925.

Calcium salts, when administered orally in amounts containing a calcium oxide equivalent of 0.2727 Gm. per kilogram of body weight, are absorbed rapidly enough to increase the serum calcium level in dogs. The tetany of parathyroprivic dogs may be controlled by increasing the blood calcium level in this way.

ARTHUR LOCKE.

FURTHER STUDIES IN THE APPLICATION OF THE CREATININ KIDNEY FUNCTION TEST. NELS F. OCKERBLAD, J. Urol. **14**:477, 1925.

The fact that creatinin is an end product of body chemistry and suffers no further chemical reduction in the body, nor, as far as is known, is stored up

by any organ or tissue, but is normally separated from the blood stream and excreted by the kidney, makes it an ideal substance for use as a test of renal function.

A persistent depressed curve is a warning that the kidney is damaged beyond recovery. With the aid of this test information may be obtained regarding the functional ability of the kidney when the phenolsulphonphthalein test is silent.

As a test for use in urology in which precise information is required in a short space of time it is unexcelled.

Its application in prostatism is of great value when used in conjunction with blood chemistry studies and the clinical signs.

AUTHOR'S SUMMARY.

THE EFFECT OF DIURETICS ON TRANSPLANTED KIDNEYS. JACKSON K. HOLLOWAY, J. Urol. **15**:111, 1926.

A series of experiments was performed on dogs in an attempt to determine the effect of diuretics, injected intravenously, on autogenous and homogenous kidney transplants. Autogenous transplants maintain viability and functional activity indefinitely, and death of the animal or disturbance of function of the transplant is due to extraneous causes. The functional activity and also the secretion of such transplants are apparently similar if not identical to those of a normal kidney. The effect of diuretics is the same as in a normal kidney.

Homogenous transplants maintain only a transient viability, and their functional activity is usually short-lived. As long as homogenous transplants remain viable, they function in a manner similar to autogenous transplants. They tend to eliminate urine which in most respects is similar to urine secreted by normal kidneys. As a rule, however, the early appearance of albumin, red blood cells and pus denotes marked parenchymatous changes within the kidney. While functioning, the homogenous transplant tends to respond to a diuretic in very much the same manner as does a normal kidney, except that diuresis is not so marked or so prolonged. Loss of function and lack of response to diuretics are apparently directly in proportion to pathologic changes within the transplanted kidney. When function has ceased, the introduction of a diuretic is without effect.

AUTHOR'S SUMMARY.

THE EFFECT OF SECTION OF BOTH SACRAL NERVES ON INTRAVESICAL PRESSURE. J. CRAIG POTTER, J. Urol. **15**:197, 1926.

Section of both sacral nerves in the dog does not affect the vesicle tone, nor the mechanism of micturition; neither does it cause retention of urine nor reflux up the ureter.

AUTHOR'S SUMMARY.

PULMONARY BLOOD PRESSURES. AN EXPERIMENTAL STUDY. J. E. SCARFF, Arch. Surg. **12**:591, 1926.

In six dogs the left pulmonary artery was ligated, and subsequent tracings were taken of the pressure in the main pulmonary artery. There is a considerable normal variation in the pulmonary systolic blood pressure in dogs. An increase of 30 to 50 per cent followed ligation of the central pulmonary artery and an increase in pulse pressure of 35 to 100 per cent. This rise eventually subsides, and the blood pressure returns to normal after from seven to twenty-one days. It was impossible to produce lung abscess or suppuration by a variety of injections into the lung tissue. The lung tissue deprived of its

blood supply appears to favor the development of effusion and adhesions. In four dogs the left lung was removed, and in these no pleural effusion developed, and in only one adhesions occurred. A description and diagram of the apparatus used to register the pressure in the pulmonary artery is given.

N. ENZER.

EFFECT OF TETHELIN ON GROWTH AND LONGEVITY. T. B. ROBERTSON and L. A. RAY, Australian J. Exper. Biol. & M. Sc. **2**:173, 1925.

Preadolescent hypodermic administration of tethelin to mice, in a dosage of 4 mg. daily, causes initial retardation, followed by compensatory acceleration of growth, which eventually leads to a considerable overgrowth of the treated animals, and which attains its maximum at about 500 days of age. The treated animals then exceed the normal animals both in size and in weight. The average life duration of the treated animals exceeded that of the controls by ninety days.

THE BASAL METABOLISM AFTER PNEUMONIA. BELA SCHICK, PHILIP COHEN and ISABELLE BECK, Am. J. Dis. Child. **31**:228, 1926.

After pneumonia, there is not infrequently a low basal metabolism which rises to normal in from one to three weeks, occasionally longer, which is associated with a slow pulse rate. Less frequently, there is a high postinfectious basal metabolism which declines to normal in from two to three weeks. Often after infections, there is a marked tendency to obesity or a leanness, or a stunting of the growth processes, which may be related to the findings mentioned in the foregoing.

AUTHORS' SUMMARY.

STUDIES ON SUPRA-VITALLY STAINED LIVING AND DEAD LEUCOCYTES AND EPITHELIAL CELLS IN THE VAGINA OF THE RAT AND THEIR RELATION TO THE OVULATION CYCLE. ALAN F. GUTTMACHER, Bull. Johns Hopkins Hosp. **38**:61, 1926.

The relative proportion of dead to living leukocytes increases in the vaginal fluid of rats after the ovulation cycle progresses from postestrus through late diestrus. The author expresses the hope that the methods used by him may be useful in the study of ovulation in other animals. It is possible that the method may bring out cyclic differences so far not detected.

STUDIES OF CERTAIN HITHERTO UNDESCRIBED ANTIRACHITIC SUBSTANCES. ANDOR DE BOSANYI, Bull. Johns Hopkins Hosp. **38**:72, 1926.

Healing of rickets may be induced by certain hitherto unrecognized antirachitic substance. These are: A histon—the globin of hemoglobin, a diamino acid—cystin—an aromatic compound—epinephrine, and an alkaloid, pilocarpine.

AUTHOR'S SUMMARY.

OBSERVATIONS ON THE EFFECTS OF LIVER EXTRACTS IN HYPERTENSION PRODUCED BY GUANIDINE COMPOUNDS. RALPH H. MAJOR, O. O. STOLAND and C. R. BUIKSTRA, Bull. Johns Hopkins Hosp. **38**:112, 1926.

An extract from the liver had marked effect in lowering hypertension caused by compounds of guanidine. This effect of the extract was apparently not due to choline, histamine or peptone.

THE SECRETION OF INORGANIC PHOSPHATE BY THE KIDNEY. II. INFLUENCE OF THE PITUITARY GLAND AND OF THE WALL OF THE THIRD VENTRICLE. L. BRULL and F. EICHHOLZ, Proc. Roy. Soc. Med. **99**:70, 1925.

Removal of the pituitary body or injury to the tuber cinereum inhibits the normal secretion of inorganic phosphates by the kidney.

ARTHUR LOCKE.

INTERAGGLUTINATION OF MATERNAL AND FETAL BLOOD IN RELATION TO ECLAMPSIA. CATHALA and LERASLE, Rev. franç. de gynéc. et d'obstét. **20**:577, 1925.

Cathala and LeRasle found in ninety-two cases of normal pregnancy that the blood of the mother and that of the new-born infant were of different groups in twenty-five; thus there was blood incompatibility in 14 per cent. Of the twenty-nine cases with pregnancy complications, the blood groups were different in the mother and fetus in only 20 per cent. Blood incompatibility was manifest in three of twenty-one pregnant women with albuminuria; in one of four with eclampsia and in one of three with uteroplacental hemorrhage. Evidently incompatibility of the maternal and fetal blood is not responsible for eclampsia or other complications in pregnancy, as in the majority of the toxemias of pregnancy investigated there was no iso-agglutination.

RESEARCHES ON THE SINO-AURICULAR PORTION OF THE CONDUCTING SYSTEM IN THE HUMAN HEART. RICCARDO SEGRE, Arch. di pat. e clin. med. **4**:308, 1925.

The author studied serial sections of four human hearts. He made a plastic reconstruction of one according to the method of Bern, and found that there is not only the part already known as the sinus node, but another much larger, situated in the groove between the two auricles. A prolongation of this part is buried in the septum between the auricles, where it pierces the left endocardium. The author concludes that one may reasonably speak of two sinus nodes, a left and a right, without being able to say whether or not they are united.

B. R. LOVETT.

ACTION OF AQUEOUS EXTRACT OF BLOOD PLATELETS ON ARTERIAL PRESSURE AND VASCULAR CALIBER. JACQUES ROSKAM, Arch. Int. de méd. expér. **1**:577 1925.

Aqueous extract of blood platelets of rabbits (extract of blood platelets of about 30 cc. of blood) given intravenously has a marked hypotensive action on the carotid pressure in rabbits and in dogs; extracts of blood platelets of dogs or of human beings have no such action.

Injected into the blood stream of an animal in toto, or added to the perfusion liquid irrigating an isolated organ, aqueous extract of blood platelets of rabbits causes a noticeable dilation of the blood vessels of the legs and kidneys of dogs. This vasodilatation may be observed directly when one applies a cotton plug, soaked with more concentrated extract, on the surface of the pancreas of a living animal.

In the same experiments, there was, on the contrary, a considerable and prolonged diminution of the volume of the spleen. An almost complete absence of capillary vessels and an extreme abundance of nonstrided muscular fibers in the arteries, veins, trabeculae and elastic coat, make the histologic structure of the spleen quite different from that of the kidney; it is more nearly related to that of the arteries. Stewart and Zucker, Le Sourd and Pagniez have shown

that extract of blood platelets of rabbits exercises a vasoconstrictor action on isolated arterial rings.

Like histamine (studied by Dale), aqueous extract of blood platelets of rabbits has a double vasomotor action: a vasoconstrictor action on the arteries and probably on the veins, and a vasodilator action on the capillary vessels.

PAUL BRUTSAERT.

FUNCTIONS OF THE GALLBLADDER. DELREZ and CORNET, Arch. Int. de méd. expér. **1**:649-674, 1925.

By means of the colorimetric method of Salkowski modified by Hooper and Wipple, Delrez and Cornet estimated the pigments of the vesicular bile before and after ligature of the neck of the gallbladder. They also compared the vesicular with the hepatic bile, and found that during its passage and sojourn in the gallbladder, the bile is markedly concentrated.

The amount of cholesterol (modified test of Grigaut, for the extraction of the cholesterol, benzol is used instead of ether) per volume unit is also increased, and relatively more than the amount of pigments. The reason for this is that when the concentration of the pigments is due only to a reabsorption of water, the concentration of cholesterol results from the same reabsorption of water and from an excretion of cholesterol out of the walls of the gallbladder.

PAUL BRUTSAERT.

HEMOPOIESIS IN ADULT ADIPOSE TISSUE. ELSE PETRI, Virchows Arch. f. path. Anat. **258**:37, 1925.

Petri made a study of the retroperitoneal adipose tissue of forty cases, chiefly of infection and sepsis, but including also examples of pernicious anemia, leukemia and neoplasia. All but nine of the group examined showed the presence in the tissue studied of small, hemorrhagic islands varying in size from that of a pinhead to that of a bean and having the appearance of hemorrhagic lymph nodes or hemolymph nodes. The islands were distinct from the latter, however, and were composed of young cells, among which could be seen evidences of lymphopoiesis, myelopoiesis and erythropoiesis, the three processes occurring either singly or combined. From such islands of formative cells, lymphoid aggregates and finally even true lymph nodes or hemolymph nodes may be formed. The adipose tissue is looked on as a mesenchymal reticulo-endothelial tissue which retains the embryonic potentialities of hemopoiesis. The latter is supposed to occur by a process of prosoplasia. The elements of the adipose tissue become dedifferentiated to embryonic individual stem cells which then by differentiation can form lymphocytes, myelocytes and erythrocytes and finally lymph nodes and hemolymph nodes. This process is believed to occur as the result of the action of toxic or bacterial stimuli.

O. T. SCHULTZ.

THE STUDY OF THE INDIVIDUAL CONSTITUTION. J. BARTEL, Ztschr. f. Konstitlhr. **11**:127, 1925.

Bartel calls attention to the fact that the study of immunology, the hereditary factors in disease and the relationship of various organ systems, as revealed by endocrinology, has enforced the necessity for the study of the age-old and difficult problem of the individual disposition to disease. He regards a knowledge of the historical development of the subject as important for a proper approach to it. The existence of a congenital disposition toward disease is

emphasized and illustrated by necropsy records, and he holds that necropsies should not be restricted to a determination of local lesions, but should be used to reveal to what extent the lesions resulted from external influences and anomalies of the individual constitution. The importance of group characters and collective observations in the attack on the problem is emphasized.

NATURE AND SIGNIFICANCE OF FEVER. R. ISENSCHMID, Schweiz. med. Wchnschr. **52**:1173, 1925. FEVER. W. LÖFFLER, ibid., p. 1181.

A large part of both articles is devoted to a review of the literature on fever. Isenschmid defines fever as a disturbance of the function of the heat-regulating apparatus, especially of the heat-regulating center in the midbrain, leading to an increase in the temperature of the body. He discusses the mechanism controlling heat production and heat loss, the location of the heat-regulating center in the base of the brain together with its efferent and afferent tracts, and the heat production during acute and chronic fevers. The changes characteristic of increased metabolism of the body during fever has been attributed to the metabolism of the infecting organism, the effect of increased body heat on chemical reactions, to increased metabolism during inanition and decrease in the glycogen content of the liver. Considerable reference is made to the experimental work on protein destruction during fever and to a lesser extent to the disturbance of metabolism of fat, water, salt and some other substances.

The discussion of the causes of fever is concise but comprehensive and includes much of the experimental data in regard to heat puncture, the effect of heat and cold on the heat-regulating center, the effect of chemical solutions acting on the surface of the base of the brain, and intravenous injection of organic substances. Few substances of known chemical composition have been found that produce fever when administered in small doses. Tetrahyero-B-naphthylamin has been used most extensively, and Cloëtta and Waser have demonstrated that the body temperature increases in the brain more rapidly than in other parts of the body following intravenous injection of this substance. Cocaine, caffeine, epinephrine and a few proteins have also been used experimentally. Of the latter substances, those that have a free amino group in the absence of a carboxyl group are most active fever producers (tyramine). Ending with the discussion of the significance of fever, Isenschmid covers theories and experimental data bearing on the three following questions: (1) Is fever itself harmful? (2) Do infected animals withstand infection better with or without fever? (3) Does fever inhibit or accelerate the production of antibodies during the infection?

In Löffler's article, there is more extensive discussion concerning the relationship of fever and anaphylaxis. There is also considerable reference to the relationship between fever and internal secretions, including the premenstrual temperature elevations, the slow and rapid rises of temperature of hypothyroidism and hyperthyroidism, respectively, during infection, epinephrine-hyperglycemia and hyperthermia, and the effect of insulin on the heat regulating center.

Hyperpyrexia associated with cerebral ventricular hemorrhage and cerebral neoplasms is in a large part probably due to the pressure on the heat regulating center in the midbrain.

C. W. APFELBACH.

THE BLOOD SUGAR IN CHRONIC PULMONARY TUBERCULOSIS. W. LANDAUER and O. GLOGAUER, Ztschr. f. Tuberk. **43**:121.

The amount of glucose in the blood drawn before breakfast is usually within the normal limits. After the ingestion of 20 Gm. of glucose some far advanced patients show hyperglycemia of abnormally long duration, which is explained as being due to a functional disturbance of the liver. Muscular activity for one half hour after the ingestion of the same amount of glucose in far advanced patients results either in a delayed and protracted hyperglycemia or in a less pronounced and shorter hyperglycemia than after complete rest. The first type of reaction is explained by an additional hyperglycemia due to an asphyctic condition of the tissue; the second type is due to a deficiency of glycogen in the tissues.

MAX PINNER.

Pathologic Anatomy

IDENTIFICATION OF THREE TYPES OF MONONUCLEAR PHAGOCYTES IN THE PERIPHERAL BLOOD. F. A. MCJUNKIN, Arch. Int. Med. **36**:799, 1925.

Monocytes, mononuclear benzidin-positive phagocytes reacting to neutral red by the method of supravital staining, are present in normal human blood, and an occasional one is present in the blood of the normal guinea-pig. These cells have not been demonstrated in rabbit blood. They are increased in the blood of the guinea-pig during the terminal stage of tuberculosis. Since they are found only in the bone-marrow and spleen, these fixed tissues are regarded as the probable source for their production.

Lymphendotheliocytes, benzidin-negative mononuclear phagocytes that by the method of supravital staining react to neutral red (sometimes with arrangement of the dye granules in the form of a roset), are present in the peripheral blood of the normal guinea-pig and rabbit and in human blood. They are increased in the blood of the rabbit by intraperitoneal injections of whole rabbit blood and in guinea-pig blood during tuberculous infection. They arise from the lymphatic reticulo-endothelium. These leukocytes become transformed into the epithelioid cells of tubercles with preservation of their characteristic reaction to neutral red.

Hemendotheliocytes, benzidin-negative mononuclear phagocytes not reacting by the method of supravital staining to neutral red or reacting slightly to neutral red with the appearance of irregular dye cytoplasmic granules, have not been demonstrated in the normal peripheral blood. They appear in the blood of the rabbit following intravenous injections of India ink. These phagocytes, which react earlier and more intensely to intravenous carbon in suspension and to colloidal dyes than do other cells, probably arise from the blood vascular endothelium.

By direct examination, therefore, three kinds of mononuclear phagocytes may be demonstrated in the circulating blood, two of which are found under normal conditions. Less direct evidence points to the conclusions that the benzidin-reacting phagocytes are derived from the bone marrow and the spleen, and that the two benzidin-negative phagocytes arise from the lymph nodes and from the endothelium of capillary blood vessels, respectively.

S. A. LEVINSON.

A Comparison of Acute Rheumatic and Subacute Bacterial Endocarditis. B. J. Clawson and E. T. Bell, Arch. Int. Med. **37**:66, 1926.

The leukocyte count is of little value in differentiating rheumatic from subacute bacterial endocarditis. A severe secondary anemia strongly suggests the subacute bacterial type. The order of frequency of valvular involvement is essentially the same in both forms. In both types there is a proliferative inflammation in the valve, but the thrombus over the infected area is larger and softer in the subacute lesion. The differences are in degree rather than in kind. Typical rheumatic vegetations may be found with subacute vegetations on the same leaflet. Myocarditis is more frequent in the acute rheumatic cases that come to necropsy. Pericarditis seems to occur with practically the same frequency in rheumatic and in subacute bacterial endocarditis. The frequent presence of embolic phenomena in the subacute bacterial type depends on the degree of involvement of the valves. Mural endocardial involvement occurs with about the same frequency in both types but is more extensive in the subacute bacterial type. The finding of bacteria in the blood stream in endocarditis does not necessarily indicate the presence of the condition clinically recognized as subacute bacterial endocarditis. Experimental endocarditis and myocarditis similar to human rheumatic lesions can be produced in rabbits by injecting streptococci. The streptococci, generally the viridans strains, seem to be responsible for both rheumatic and subacute bacterial endocarditis.

S. A. Levinson.

Mycosis Fungoides. J. Frank Fraser, Arch. Dermat. & Syph. **12**:814, 1925.

Two cases are added to the growing number of instances of mycosis fungoides in which the pathologic changes in the tissues are unquestionably neoplastic.

Evidence is presented which shows a genetic relation between mycosis fungoides, lymphatic leukemia and lymphosarcoma.

The name reticulum cell sarcoma is suggested to replace the term lymphosarcoma in designating the lesion of mycosis fungoides. The suggestion is based on the assumption that the lesion has its origin in the reticulum cells of the papillary layer (reticulo-endothelial system of the skin).

Author's Summary.

Ulcus Vulvae Acutum (Lipschütz). Clark W. Finnerud, Arch. Dermat. & Syph. **13**:55, 1926.

In ulcus vulvae acutum (Lipschütz) we have to deal with a comparatively newly described nonvenereal genital infection of acute onset and self-limited course. The ulcers occur in "gangrenous" and "venereal" types. In the former, fever and other constitutional symptoms occur at the onset of the disorder. The lesions in this type are few, varying in size from that of a pea to that of a coin, tender, deep, soft, with fibrinopurulent coating, red areola and with predilection for the inner surface of the small labia. They heal in about two weeks, with scar formation. In the venereal type there are usually no constitutional symptoms, the lesions are usually smaller, shallower, more numerous, most common about the vaginal introitus, and the course is more chronic. Various factors capable of lowering the patient's local tissue resistance apparently render the saprophytic *Bacillus crassus* pathogenic. This organism is apparently identical with Döderlein's vaginal bacillus and is ever-present in

the lesions, existing as a thick (0.5 micron) and usually long (3 to 9 microns), gram-positive bacillus with ends sharply right-angled to its long axis. It is easily demonstrated in smear preparations from the ulcer surface and can be cultivated with but little difficulty, aerobically and anaerobically, on maltose-ascitic-fluid agar and sugar-serum-agar. This disease occurs chiefly in persons between the ages of 14 and 20 years, and is more common in virgins than in others.

AUTHOR'S SUMMARY.

GROSS AND HISTOLOGIC CHANGES IN THE EDEMA OF PARAPHENYLENEDIAMINE. M. L. TAINTER and E. M. HALL, Am. J. Path. **1**:503, 1925.

The systemic administration of paraphenylendiamine hydrochloride to rabbits and cats produced a marked and apparently specific edema in the tissues of the head and neck, characterized by a wide separation of the tissue elements and extensive precipitation of fibrin. Local applications of alcoholic and aqueous solutions of the base to the skin in rabbits produced a marked local edema.

L. HEKTOEN.

EXPERIMENTAL HYDRONEPHROSIS. THE EFFECT OF CHANGES IN BLOOD PRESSURE AND IN BLOOD FLOW ON ITS RATE OF DEVELOPMENT AND THE SIGNIFICANCE OF THE VENOUS COLLATERAL SYSTEM. PARTIAL OBSTRUCTION OF THE RENAL VEINS WITHOUT AND WITH LIGATION OF ALL COLLATERAL VEINS. F. HINMAN and A. B. HEPLER, Arch. Surg. **11**:917 (Dec.) 1925.

Partial obstruction of the renal vein causes an increased intrarenal and secretory pressure. The development of hydronephrosis following ureteral obstruction is accelerated by partial obstruction of the renal vein. This is true until the collateral venous circulation is established, from which time the rate of development is very much the same. The development is still more accelerated if in addition to partial obstruction of the renal vein the venous collateral circulation is destroyed. In the latter secondary atrophy and shrinkage take place at the time the venous collateral circulation would have been established normally. The action of the venous collateral system is not an essential to the development of simple hydronephrosis, but its failure is probably the cause of the secondary atrophy and shrinkage sometimes found following hydronephrosis.

N. ENZER.

THE OSTEOGENETIC FUNCTION OF THE PERIOSTEUM. F. E. BLAISDELL, Arch. Surg. **11**:933 (Dec.) 1925.

From a study of the bones of human fetuses of different age periods the author concludes that the perichondrium antedates and later becomes the periosteum, and that the first bone is deposited as subperichondriac bone by the perichondrium, and the osteogenesis of bone is later taken over by the periosteum. The origin of the osteoblasts and the possibility of their development from the fibroblasts of the periosteum is discussed. The article is illustrated by photomicrographs.

N. ENZER.

STRATIFIED SQUAMOUS CELL CARCINOMA OF THE BODY OF THE UTERUS. E. F. HIRSCH, Arch. Surg. **11**:957 (Dec.) 1925.

Three cases of squamous cell carcinoma of the fundus of the uterus are presented in summary and the literature reviewed. These tumors contained

hornified cell masses, and the epithelium was proliferating in stratified layers. They may contain both columnar and squamous epithelium in varying proportions.

N. Enzer.

Congenital Cystic Lung. R. T. Miller, Arch. Surg. **12**:302, 1926.

Anomalies of the lung are rare. Two cases are presented, in one of which necropsy demonstrated a cystic lung in a child dying on the twelfth day after delivery. From the clinical signs, he concludes the condition to have been the same in the other case, although no necropsy was obtained. These cysts are lined by flat and cuboidal epithelium and frequently communicate with each other and with the bronchioles but not with alveoli. Rupture of these cysts causes spontaneous pneumothorax. Many speculations on their origin have been offered, no one of which is adequate.

N. Enzer.

Gaucher's Disease: Report of a Case Showing Bone Disintegration and Joint Involvement. E. H. Cushing and A. P. Stout, Arch. Surg. **12**:539, 1926.

In a clinical review of the aspects of Gaucher's disease, the authors present two cases, in one of which there was an associated osteo-arthritis with destruction of the head of the femur and acetabulum. Three months after splenectomy, removal of the head and neck of the femur was done. The specimen showed softening of the bone, wide marrow spaces which on section proved to be filled with cells in every way similar to the large Gaucher cells of the spleen. This case illustrates the fact that changes in Gaucher's disease are not limited to the spleen, and the question arises whether or not splenectomy prolongs life or merely relieves the aggravation of the large spleen.

N. Enzer.

Coarctation of the Aorta. James W. Bruce and Robert Ball, Am. J. Dis. Child. **31**:196, 1926.

It is noteworthy that in this case intermittent cyanosis, irrgular respiration and convulsions were caused probably by marked narrowing of the aorta just beyond the origin of the branches to the heart.

Parkinsonian States: Clinicopathologic Studies. G. B. Hassin and Peter Bassoe, Arch. Neurol. & Psychiat. **12**:218, 1926.

The parkinsonian states, though of different nature, have in common the clinical picture of paralysis agitans and lesions in the basal ganglions and substantia nigra. In classic paralysis agitans the lesions are degenerative, while in the postencephalitic forms the lesions are degenerative and inflammatory.

The Type of Phagocytic Cell and Its Relative Proportions in Human Bone Marrow and Spleen, as Identified by the Supravital Technique, with Special Reference to Pernicious Anemia. Charles A. Doan, J. Exper. Med. **43**:289, 1926.

In general, there is a reversal of the normal in the ratio of clasmatocytes in the spleen to clasmatocytes in the bone marrow in pernicious anemia, with a marked tendency toward the phagocytosis of young, immature, nucleated red blood cells in the bone marrow. The peripheral blood picture suggests that

these cells have never been in circulation. The observations made do not indicate that the spleen takes any directly active part in an increased destruction of the blood in pernicious anemia.

AUTHOR'S SUMMARY.

EFFECTS OF INSULIN ON THE WEIGHT OF THE RABBIT'S SUPRARENAL GLANDS. HARVEY S. THATCHER, J. Exper. Med. **43**:357, 1926.

There is no gross hypertrophy of the suprarenals in rabbits after long continued, daily doses of insulin.

AUTHOR'S SUMMARY.

COMPENSATORY HYPERTROPHY OF THE ADRENAL CORTEX. EATON M. MACKAY and LOIS LOCKARD, J. Exper. Med. **43**:395, 1926.

Removal of one suprarenal in the albino rat is followed by hypertrophy of the remaining gland. In the case of female rats, 90 days of age, this compensatory hypertrophy amounted to 61 per cent. The increase in size of the whole gland is due entirely to hypertrophy of the cortex. This increase in cortical tissue amounted to approximately 91 per cent, and was due largely if not entirely to an increase in the size of the cells. No increase in the size of the medulla or its cells was found.

AUTHORS' SUMMARY.

STUDIES ON THE HISTOGENESIS OF AUTOPLASTIC THYMUS TRANSPLANTATIONS. JESSIE M. GOTTESMAN and HENRY L. JAFFE, J. Exper. Med. **43**:403, 1926.

The thymus gland of young rats autotransplants easily when inserted in the muscles of the abdominal wall. Destructive changes take place during the first forty-eight hours, when regenerative changes set in. The regeneration is usually complete by the fourteenth day, when the newly formed thymic lobules show differentiation into cortical and medullary zones. The small thymic cells arise from the reticular epithelium in the regeneration of the transplant.

AUTHORS' SUMMARY.

A STUDY OF THE URINARY TRACT IN AUTOPSY SPECIMENS. CORRELATION OF ANATOMY, PATHOLOGY AND ROENTGENOLOGY. ALBERT E. GOLDSTEIN and WILLIAM J. CARSON, J. Urol. **15**:155, 1926.

The normal human ureter varied from 1.5 to 7 mm. in diameter; the normal renal pelvis measured from 1 by 0.8 cm. to 3 by 2 cm.; the capacity of a normal ureter, pelvis and calixes varied from 5 to 13 cc., the average being 8 cc. Ureter, pelvis and calixes considered normal in an ureteropyelogram as interpreted by these measurements showed no pathologic changes; if considered pathologic in the ureteropyelogram, changes were demonstrated.

PHLEBOLITHS. JOHN M. CULLIGAN, J. Urol. **15**:175, 1926.

With the development of the roentgen ray, phleboliths became clinically significant. They are seen most frequently in roentgenograms of the pelvis and at necropsy; 38.99 per cent of pelvic roentgenograms at the Mayo Clinic show shadows of phleboliths. The shadows were two-thirds as common in females as in males. Forty-seven per cent of shadows of phleboliths were bilateral.

The phleboliths vary between 1 and 10 mm. in diameter, the average being about 4 mm. They are found most frequently in the periprostatic plexus of

males and in the uterine plexus of females; occasionally they are found in splenic veins and in the veins of hemangiomas.

Microscopically, phleboliths are strikingly uniform, the main difference being that the larger ones show areas of ossification. Their chemical analysis shows that they contain practically uniform ingredients.

Phleboliths have their origin in thrombi. The chief factors in their formation are lack of muscular support to the veins, stasis, undernourishment, infection and calcification.

The shadows of phleboliths are easily confused with the shadows of ureteral stones. Roentgenologists can determine in about 94 per cent of cases whether pelvic roentgenographic shadows are due to phleboliths. Urologists should be able to identify all pelvic shadows as extra-urinary or intra-urinary.

The lead catheter is unreliable in localizing pelvic shadows. Pyelography is the most accurate method known for localizing questionable pelvic shadows. The perivesical plexus containing phleboliths and thrombi is an ever ready focus for emboli.

AUTHOR'S SUMMARY.

PATHOLOGY OF CORONARY ARTERY DISEASE. R. L. BENSON and W. C. HUNTER, Northwest Med. **24**:606, 1925.

Two hundred instances of advanced coronary obstruction were selected by Benson and Hunter from 1,750 necropsies. In 145 hearts, emboli or fresh thrombi or old thrombi or combinations of these were demonstrated. In ninety-four hearts, fresh thrombi were present in one or more coronary arteries or their branches. Only forty of the ninety-four contained either definite infarcts or cardiac aneurysms, although a few more contained patchy necroses. Thus, fifty-four had fresh coronary thrombosis without infarction or aneurysm, and it is probable that most of these represent death in the first attack before an anatomic infarct had had time to form. In seventy hearts, the coronary arteries contained either old obliterative or recanalized thrombi, or types of obliterative endarteritis closely simulating these. Aneurysms of the left ventricle occurred in nineteen, and healed infarcts without formation of aneurysm in eleven cases. Embolism contributed fourteen instances of coronary occlusion, nine of which resulted in infarction. The other five comprise cases which resulted fatally before the anatomic evidences of infarction could manifest themselves. The total number of acute infarcts collected is forty-six; healed infarcts, eleven, and cardiac aneurysms, nineteen; total (after deduction for four duplications), seventy-two infarcts and aneurysms. Definite indisputable aortic syphilis was present in thirty-five, or 17.5 per cent, of the 200. Among the thirty-five hearts accompanied by a definite syphilitic aorta, ten manifested acute coronary thrombosis, five old coronary occlusions, and six contained infarcts; but the number of such cases was not determined. Rupture of the heart, always of the left ventricle, occurred in fourteen cases, exactly one half of which fall in the definitely syphilitic class. One rupture occurred through the septum interventriculorum into the right ventricle; the others, into the pericardial sac. Acute infarcts caused seven deaths; syphilitic myocarditis, three; rupture of a syphilitic coronary with resulting myocardial apoplexy, and rupture of dissecting coronary aneurysm, one death each.

ISCHEMIC NECROSIS OF HEART MUSCLE. A. G. GIBSON, Lancet **2**:1270, 1925.

Forty-three instances of various clinical types of ischemic necrosis are analyzed by Gibson. Sudden death occurred in seven; angina was the dominant

symptom in sixteen cases. In six cases, the symptoms were those of chronic heart failure. Abdominal symptoms and collapse were present in eight cases; four cases did not present any cardiac symptoms. One patient had fainting attacks and died suddenly, and in one case delirium and failing pulse were present for three days before death. In all these cases, blockage of an artery and consequent change in the heart wall was found at the necropsy.

POSTMORTEM PHAGOCYTOSIS. W. SIEMENS, Beitr. z. path. Anat. u. z. allg. Pathol. **73**:626, 1925.

Siemens claims that the introduction of India ink, staphylococci and thrush fungus into the nasal cavity immediately after death is followed by active phagocytosis of the foreign material by intravascular phagocytes for a period of sixty-eight hours postmortem.

O. T. SCHULTZ.

GENERALIZED EDEMA OF THE NEW-BORN. M. GOORMAGHTIGH, Ann. d'anat. path. méd.-chir. **2**:413, 1925.

Schridde is given credit for launching this disease as an entity in 1910. It has been regarded as a form of pernicious anemia, but in this study from the Pathological Institute of the University of Ghent, it is definitely placed with the leukemias.

Most severe anemias are attributed to an absence or disease of the spelialized tissues in bone marrow or other places in which red blood cells have their origin, or to destruction of such cells after they are formed in a normal way. The anemia of this congenital edema, by this report, is given a new cause, embryonic red cells in the blood, their failure to mature and their inability to transport oxygen as do normal erythrocytes.

The only red cells in the blood were nucleated, and they formed 34.5 per cent, large primitive blood cells [hematogonien] the next in abundance, 18.5 per cent.

The most active myeloid foci were about the portal vessels in the liver, as sheaths for the renal arteries all the way out to the glomeruli, under the lining of the renal pelves and in the placental villi. Less active were those in the thymus, spleen, lymph glands, suprarenal glands and lungs. These places where cells normal and abnormal for the blood stream were originating and developing were not all primary, those of the suprarenal glands and lungs, for example, being embolic; nor was the hematopoiesis in any of them strictly erythrocytogenesis.

New capillaries formed in the placenta and, possibly in response to the needs of the embryo for more oxygen, gave to that organ an angioma-like structure. The proliferation of endothelium in pulmonary capillaries together with their occlusion by large phagocytic macrophages markedly distorted the structure, and if present with birth at the normal time, presumably would have seriously impaired or altogether prevented respiration.

It is a matter of some regret that the conditions described by Goormaghtigh were in a fetus of 6 months' gestation (live birth induced for hydramnios) and not from later development. It is suggested that this limitation, however, is somewhat controlled by other reports of the disease.

The edema is secondary to the anemia, hence the name the disease has come to bear is essentially infelicitous and inappropriate. Toxic agents and infection are urged as its cause in place of nephritis in the mother, and attention is called to the similarity it possesses to acute rather than to chronic leukemias, and to the infectious leukemia of fowls.

E. R. LECOUNT.

THE REASONS FOR THE CHRONICITY OF GASTRIC ULCER. W. SIEMENS, Beitr. z. path. Anat. u. z. allg. Pathol. **73**:630, 1925.

Thrush fungus, which Askanazy and others have held to be an important factor in the nonhealing of chronic gastric ulcer, is only a secondary surface contamination according to Siemens. The vascular changes seen in chronic gastric ulcers are secondary, but may help to prevent healing because of abnormalities in circulation. The hydrochloric acid of the gastric juice is held to be the chief and primary factor in the nonhealing of ulcer; the acid causes necrosis of the exposed granulation tissue and may interfere with healing also by causing spasm of the blood vessels.

O. T. SCHULTZ.

THE ELASTIC SYSTEMS ESPECIALLY OF THE AORTIC WALL. O. RANKE, Beitr. z. path. Anat. u. z. allg. Pathol. **73**:638, 1925.

Ranke applies mathematical and mechanical concepts to an analysis of the function of the elastic tissue of the aorta. He concludes that elasticity in the usual sense is only one of the functions, and perhaps not the most important one, of this tissue, and is probably no greater than the elasticity of the collagen fibers. Because of the fixed, undulating course of the elastic fibrils in the wall of the aorta, the tissue exerts mechanical actions which Ranke likens to those of a steel coil spring rather than of a rubber band. It stiffens and supports the wall, protecting the other tissue elements against overdistention. The distensibility of the aorta and the return of the latter to an undistended or resting state depend on the springlike action which their fixed curves give to the elastic fibers. The mechanical action of the elastic tissue of the aorta is compared with that of the lung, in which the fibrils have a more direct course and act like a sliding lattice-work.

O. T. SCHULTZ.

LOCALIZATION OF RACHITIC CHANGES IN THE CRANIUM. H. BENDIXEN, Beitr. z. path. Anat. u. z. allg. Pathol. **74**:103, 1925.

Bendixen interprets the rachitic thickenings of the skull in the light of the findings of Pommer, Schmorl, Beneke and others in the long bones, in which the areas of rachitic proliferation occur at points where the bones are subjected to static and mechanical forces. In the skull thickening occurs, not at some one or other indefinite point, but in areas which are subjected to mechanical stress. Since the skull is a closed spheroid, the pressure exerted by the weight of the head, especially in the recumbent position, is transmitted along the main radii of the skull to points opposite that at which the pressure is applied as well as at the latter point. Bendixen believes that rachitic proliferation is a delicate measure of the localization of the influence of mechanical factors acting on the bones.

O. T. SCHULTZ.

CHANGES FOLLOWING INJECTION OF PARAFFIN. C. VAN GELDEREN, Virchows Arch. f. path. Anat. **257**:805, 1925.

In an experimental study of the reaction of the subcutaneous tissue of the dog to injected soft paraffin, van Gelderen found that the injected material is not enveloped or transported. The vacuolated cells seen about the paraffin are not cells which have taken up the material, but are leukocytes and fibroblasts which have undergone fatty degeneration. The paraffin stimulates the surrounding tissue to a low grade inflammatory reaction, which tends to encapsulate

the foreign material and prevent its resorption. The paraffin therefore acts as a constant irritant, as is manifested by the degenerated cells present in the older granulation tissue and by the progressive fibroblastic proliferation.

O. T. SCHULTZ.

INFLAMMATORY PHENOMENA IN MOLLUSCS. B. KEDROWSKY, Virchows Arch. f. path. Anat. **257**:815, 1925.

Kedrowsky studied the reaction of the foot muscle of the fresh water mussel to aseptically implanted bits of celloidin. His results are preceded by a description of the blood cells and of the normal foot tissues of the species with which he worked. He divides the reaction to the implantation into an inflammatory and a regenerative stage. With the exception of degenerative changes in the injured tissues, the inflammatory reaction consists entirely of a wandering of amebocytes, which unite to form a syncytium about the foreign body. He disagrees with Morgan and Drew that the outer layer of the syncytium is formed from connective tissue cells, and there was no evidence of formation of connective tissue from the syncytium. In the regenerative process the amebocytes which have surrounded the degenerative muscle fibers become immobile and differentiate to form new connective tissue. Some of the latter tissue is also derived from the preexisting connective tissue cells.

O. T. SCHULTZ.

INFLUENCE OF THE ROENTGEN RAYS ON PROTOPLASM. S. S. WAIL and S. R. FRENKEL, Virchows Arch. f. path. Anat. **257**:846, 1925.

In the liver of frogs subjected to roentgen-ray irradiation, changes in the mitochondria can be detected before any nuclear alterations can be seen or before cytoplasmic alterations can be detected by the usual histologic methods. The early mitochondrial changes noted are not necessarily evidence of cell damage, nor are the authors willing to interpret them as indicative of cell stimulation.

O. T. SCHULTZ.

LYMPHOID CHANGES IN CHRONIC APPENDICITIS. P. HEILMANN, Virchows Arch. f. path. Anat. **258**:52, 1925.

On the basis of surgical material, Heilmann investigated the problem of changes in the appendix which might be considered characteristic of the rather indefinite syndrome which the surgeon terms "chronic appendicitis." He believes that the lymphoid follicles show such changes. The simplest form of involvement described as due to the action of a low-grade chronic irritant is enlargement of the germinal centers of the follicles, transforming the latter into so-called secondary follicles of Flemming or the reaction centers of Heilmann. It is noted that such germinal centers are indicative of chronic reaction only in adults, since they are normal for young individuals. In somewhat more advanced grades the enlarged centers contain "tingible bodies" within the cells of the center. Some of the nuclei are pyknotic. The nuclear membrane may be hyperchromatic and necrobiosis of individual cells may be noted. These lymphoid changes are associated with increase in and hyalinization of the connective tissue of the submucosa. In a third stage, fibrosis of the submucosa becomes more marked, and increase in the reticulum of the enlarged germinal centers of the follicles is evident. Small groups of lymphocytes are present in the wall, especially in the submucosa. The germinal center of the lymphoid

follicle is looked on, not as the center of formation of lymphocytes, but as the site of destruction of lymphocytes which have been injured by toxins.

O. T. SCHULTZ.

BONE MARROW CHANGES AND THE ARNETH LEUKOCYTIC FORMULA. T. YAMAMOTO, Virchows Arch. f. path. Anat. **258**:62, 1925.

By means of comparative studies of the Arneth leukocytic formula in the peripheral blood and of changes in the bone marrow in a group of infectious diseases, Yamamoto attempts an interpretation of the altered peripheral leukocytic formula. Arneth had looked on the phenomenon described by him as the result of the destruction of older leukocytes in the peripheral blood by toxic agents, the alteration of the leukocytic formula being due to the secondary entrance of younger leukocytes into the blood. Naegeli, in turn, believed the blood picture to be the result of increased marrow function. Schilling, finally, looked on the changes in the peripheral blood as secondary to histologic rather than purely functional changes in the marrow, brought about by a toxic agent. Yamamoto's studies lead him to accept this view of Schilling, Arneth's theory of peripheral destruction of older leukocytes having only a minor part in the changes noted. The formula which Arneth considered characteristic of the acute infectious diseases with supposed rapid destruction of older leukocytes is the result of active proliferative and regenerative changes in the marrow. The leukocytic picture of the chronic infections characterized by an increase in leukocytes with deeply stained rodlike nuclei is the expression of a marrow in which pathologic cell formation has become adapted to the action of the chronic irritant.

O. T. SCHULTZ.

ANEURYSM OF DUCTUS BOTALLI. E. HAMMERSCHLAG, Virchows Arch. f. path. Anat. **258**:1, 1925.

Hammerschlag describes an aneurysm of the ductus botalli in a 51 year old woman who had suffered with generalized sepsis and ulcerative endocarditis. The aneurysm was believed to be mycotic in origin. Of thirty-one previously reported cases, Hammerschlag accepts only seventeen as true aneurysms of the ductus itself. Most of the reported cases had occurred in children, the aneurysms being small, sacular dilatations of an open ductus.

O. T. SCHULTZ.

CONGENITAL ELEPHANTIASIS OF ABDOMINAL SKIN. S. KOBAYASHI, Virchows Arch. f. path. Anat. **258**:9, 1925.

In a child dying on the eleventh day after birth of urinary tract infection and meningitis, there was noted at birth a peculiar folded, wrinkled and thickened condition of the skin of the abdomen. Microscopic examination showed the thickening to be due to hyperplasia of the corium. Although the abdominal musculature appeared relatively thin, there was no actual defect of the muscle as occurs in the congenital symmetrical defect of the abdominal musculature described by Stumme, Pels-Leusden and others. The walls of the urinary bladder, ureters and rectum were also thick and hypertrophic. The condition is explained as a developmental anomaly due to some factor acting at that stage of embryogenesis when rectum and bladder are still united in the cloaca, and the anterior wall of the future bladder is in contact with the lower abdominal wall. This corresponds to the 5 to 6 mm. stage of the human embryo.

O. T. SCHULTZ.

A Case of So-Called Endophlebitis Hepatica Obliterans. Erik Böttiger, Acta Paediat. **5**:144, 1925.

A girl, 3 years old, vomited, had rapidly developing ascites and enlargement of the liver without jaundice. Death was hastened by cerebral thrombosis and softening. The cause of the ascites was extensive thickening with thrombosis in the hepatic veins. Since Chian in 1899 first described the condition illustrated by this case, thirty-one cases have been reported. The causation of the process in the hepatic veins is undecided and under discussion.

Pathologic Chemistry

The Diagnostic Criteria of Chronic Parathyroid Insufficiency with Special Reference to the Phosphate Content of the Blood. L. Berman, Am. J. M. Sc. **171**:245, 1926.

There is an increased phosphate and a slightly decreased calcium content in the blood of persons with chronic parathyroid insufficiency.

Arthur Locke.

The Excretion of Lactic Acid in the Urine After Muscular Exercise. S. H. Liljestrand and D. W. Wilson, J. Biol. Chem. **65**:773, 1925.

The total additional quantity of d-lactic acid excreted after from two to three minutes of stair running varies from 140 to 1,370 mg. A second period of exercise following shortly after the first yields similar quantities.

Arthur Locke.

The State of the Serum Calcium in Experimental Hypo- and Hypercalcemia. A. R. Moritz, J. Biol. Chem. **66**:343, 1925.

Increase in serum calcium produced by injections of parathyroid extract is not accompanied by any consistent changes in the diffusible colloidal serum calcium ratio. The decrease in serum calcium which occurs following thyroparathyroidectomy is disproportionately great in the diffusible calcium fraction.

Arthur Locke.

Studies of Methemoglobin Formation. D. D. Van Slyke and E. Vollmund, J. Biol. Chem. **66**:415, 1925.

Aniline, ferricyanide and nitrite convert hemoglobin into methemoglobin in the presence of air. Nitrite and aniline penetrate into the cells, but methemoglobin formation by ferricyanide, in vitro, occurs only after the cells are laked. The conversion caused by aniline is due to a product of aniline rather than to the material itself. Anemia caused by the absorption of nitrobenzene is not accompanied by methemoglobinemia, nor does nitrobenzene, in vitro, act on blood to produce methemoglobin.

Arthur Locke.

Studies on Cholesterol. I. Synthesis of Cholesterol in the Animal Body. F. S. Randles and A. Knudson, J. Biol. Chem. **66**:459, 1925.

The cholesterol content of adult rats, raised on a cholesterol-free diet, is many times as great as it is at birth.

Arthur Locke.

THE RELATION BETWEEN COLORIMETRIC READING AND TRUE p_H OF SERUM OR PLASMA. J. H. AUSTIN, W. C. STADIE and H. W. ROBINSON, J. Biol. Chem. **66**:505, 1925.

A method is outlined for determining the difference between the p_H of diluted serum or plasma and the true p_H of the undiluted material at 38 C.

ARTHUR LOCKE.

QUANTITATIVE CHANGES IN TISSUE GLYCOGEN BLOOD SUGAR, PLASMA, INORGANIC PHOSPHATES AND BLOOD LACTIC ACID IN CANINE HISTAMINE SHOCK. ELEANOR K. CHAMBERS and K. W. THOMPSON, J. Infect. Dis. **37**:229, 1925.

During the first fifteen minutes of canine histamine shock, there is a decrease of nearly 80 per cent. in the glycogen content of the liver, and a 60 per cent. decrease in the glycogen content of heart muscle and skeletal muscle. During the first thirty minutes of canine histamine shock, blood sugar increases about 200 per cent., blood lactic acid about 133 per cent., plasma inorganic phosphates about 50 per cent.

These changes are similar to the changes reported by O'Neill and McCullough in canine anaphylaxis, and differ from them mainly in that the maximum changes are not reached until the end of thirty minutes instead of at the end of fifteen minutes as in anaphylaxis.

No conclusion can be drawn from these data as to the relation between histamine and anaphylactic shock, but findings are not inconsistent with the view that the essential or dominant factor in canine anaphylaxis is the liberation of histamine-like substances by the liver.

AUTHORS' SUMMARY.

MUSCULAR EXERCISE, LACTIC ACID, AND THE SUPPLY AND UTILIZATION OF OXYGEN. XIII. THE CASEOUS EXCHANGES OF RESTRICTED MUSCULAR EXERCISE IN MAN. K. FURUSAWA, Proc. Roy. Soc. B **99**:155, 1926.

The oxygen intake during the exercise of a very small amount of muscle tissue rises more slowly to its maximum value than it does during exercise involving the greater portion of the musculature of the body. The oxygen intake may still be rising rapidly after six minutes of such exercise, indicating that a large oxygen debt has been set up. The lactic acid produced in excess by the violent activity of a localized group of muscles may diffuse from them into the blood, and from there to other parts of the body, particularly to the resting muscles and the liver, where it may be removed or restored to glycogen under the influence of the oxidations occurring in these other tissues. There may be a type of exhaustion due to a complete using up of the lactic acid precursor when exercise is restricted to a small group of muscles.

XIV. THE RELATION IN MAN BETWEEN THE OXYGEN INTAKE DURING EXERCISE AND THE LACTIC ACID CONTENT OF THE MUSCLES. C. N. H. LONG, ibid., p. 167.

In man, as well as in isolated muscle tissue, the rate of lactic acid removal, as measured by the oxygen intake, is proportional to the square of the lactic acid concentration in the fluids which are in contact with the muscle fibers.

ARTHUR LOCKE.

THE HYDROGEN-ION CONCENTRATION AND OXIDATION-REDUCTION POTENTIAL OF THE CELL-INTERIOR BEFORE AND AFTER FERTILIZATION AND CLEAVAGE: A MICRO-INJECTION STUDY ON MARINE EGGS. J. and D. M. NEEDHAM, Proc. Roy. Soc. B **99**:173, 1926.

The internal p_H of eggs is approximately 6.6. It is not changed by fertilization, by local injury, or by the morphologic degenerations produced in asphyxia until cytolytic stages are reached. On cytolysis the p_H falls to a point between 5 and 4. There are no rhythmical changes subsequent to fertilization, and the p_H remains constant as far as the 16 cell stage. The r_H of cells varies from 19 to 22. It is not changed on fertilization or cytolysis and is constant to the 8 cell stage. The method of micro-injection gives results diametrically opposite to those obtained by the method of vital staining.

ARTHUR LOCKE.

THE SURFACE TENSION OF TRANSUDATES AND EXUDATES. D. ADLERSBERG and O. STERNBERG, Klin. Wchnschr. **4**:2398, 1925.

The surface tension values are clinically useful in the differentiation of transudates and exudates. Values in excess of 870 (referred to water as 1,000) indicate transudates. Lower values indicate exudates.

ARTHUR LOCKE.

THE PRESENCE OF AROMATIC OXY-ACIDS IN NORMAL BLOOD. E. BECHER, S. LITZNER and F. DOENECKE, München. med. Wchnschr. **72**:2009, 1925.

There is an appreciable quantity of free, aromatic oxy-acids in normal blood.

ARTHUR LOCKE.

THE XANTHOPROTEIC REACTION. M. V. LEMESIC and BR. JOVANOVIC, München. med. Wchnschr. **72**:2142, 1925.

The urea and xanthoprotein content of deproteinized serum rises gradually and somewhat proportionately from the normal after artificial production of uremia. The xanthoprotein urea ratio is much below the normal in nephritis.

ARTHUR LOCKE.

CHEMICAL DIFFERENTIATION OF RACES. E. O. MANOILOFF, München. med. Wchnschr. **72**:2186, 1925.

Manoiloff adds to 3 cc. of a 3 to 5 per cent emulsion of blood cells (obtained from the clot) one drop of a 1 per cent alcoholic solution of methylene blue. After stirring, he adds 5 drops of a 1 per cent alcoholic solution of cresyl violet and stirs again. He adds 3 drops of a 0.5 to 1 per cent solution of silver nitrate and, after stirring, 1 drop of a 40 per cent solution of hydrochloric acid. After stirring well, he adds 3 to 5 or more drops of a freshly prepared aqueous 1 per cent solution of potassium permanganate. The amount of the latter depends on the quality of the dyes. He finds that the cresyl violet disappears in the blood taken from Jews, which becomes blue, while the fluid stays bluish red with blood from Russians. He had 187 correct results in 202 tests. He found differences even between the blood of Russians and Ukrainians. The children from mixed marriages (father Russian, mother Jewish, Polish or Armenian) gave a faster reaction than pure Russians. No difference from the Russian was noted in children from intermarriage between Russians and the German or yellow race. Kogan observed with this method that injection of

epinephrine induces temporarily the "Russian" reaction in Jewish children. He explains the differences by greater speed of oxidation in Jewish blood as compared with the Russian.

DISTRIBUTION OF COLLOID METALS IN TISSUES. I. VOIGT, Virchows Arch. f. path. Anat. **257**:851, 1925.

Voigt studied the distribution of a number of metals in the tissues of rabbits after intravenous injection of the colloid hydrosols of the metals. The fresh tissues were fixed in formaldehyde, which reduced the metals and rendered them insoluble. The author attempted to make a differentiation between the material which had been stored within cells as the result of a vital process and the diffuse metal precipitated by the formaldehyde. All of the metals used were vitally stored by the liver cells. The phagocytes stored gold, silver, silver iodin, mercury and selenium, but not manganese, copper and bismuth. Gold, silver iodin and silver were stored by the cells of the reticulo-endothelial system.

O. T. SCHULTZ.

OXIDASE REACTION OF BLOOD OF LOWER ANIMALS. G. MAY, Virchows Arch. f. path. Anat. **257**:868, 1925.

May found the pseudo-eosinophils to be the only blood cells which give the oxidase reaction in birds, whereas all of the cells of the myeloid series of the mammalia, reptilia and amphibia examined reacted positively.

O. T. SCHULTZ.

NATURE OF MALARIA PIGMENT. M. KÓSA, Virchows Arch. f. path. Anat. **258**:186, 1925.

Kósa claims that the pigment present in the reticulo-endothelial cells in malaria gives the iron reaction after preliminary treatment with alkali. The free pigment and that present in infected erythrocytes give the iron reaction after treatment with gastric juice or with concentrated acids. The greater part of the pigment is related to hematin, a smaller part to hemosiderin.

O. T. SCHULTZ.

DYSOXYDATIVE CARBONURIA. A. BICKEL and O. KAUFFMANN-COSAL, Virchows Arch. f. path. Anat. **259**:186, 1926.

The authors apply the term dysoxydative carbonuria to disturbances of metabolism characterized by increased urinary carbon excretion with an increased C:N quotient of the urine. The increased carbon is not a constituent of any specific substances in the urine but is derived from compounds in the intermediary metabolism of fats, carbohydrates and proteins which normally should be so completely oxidized that their carbon is excreted with the carbon dioxide of the lungs. The decreased tissue oxidation which leads to raising of the urinary carbon output may be due to abnormal oxygen supply to the cells, to cellular intoxication, or to deficiencies in the supply of hormones, vitamins and possibly ions to the tissues. In some cases of carbonuria without glycosuria the high C:N quotient is lowered by insulin, indicating, according to the authors, a disturbance chiefly of intermediate carbohydrate metabolism.

O. T. SCHULTZ.

A Case of Acute Spontaneous Porphyruria. Ernst Melkersson, Acta med. Scandinav. **63**:153, 1925.

Porphyruria is a relatively rare pathologic state occurring in men and animals, and characterized by an increased elimination of porphyrin in the urine and feces. Melkersson discusses briefly some theories of the origin of porphyrin, and favors the idea that porphyrin is synthesized in the intestines from the bile pigments and is nearly totally decomposed in the liver, a small part only escaping this destruction and being excreted in the urine and feces. Porphyruria is accompanied in most cases by the excretion of urofuscine, a pigment, which is responsible for the red-brown to brown-black color of the urine which is characteristic of porphyruria. An increased elimination of porphyrin is thought to be due frequently to liver insufficiency, the undestroyed porphyrin being excreted in the urine and bile. Melkersson cites experimental work, confirming the latter theory, in which porphyruria was produced in animals by phosphorus poisoning, and porphyrin was destroyed in the urine by adding fresh liver tissue.

The following clinical groups are discussed briefly: (1) the state of porphyrism; (2) congenital porphyruria; (3) chronic porphyruria, and (4) acute toxic porphyuria (sulphonol, barbital [veronol] lead poisoning).

Acute spontaneous porphyruria is discussed in more detail. It, by definition, is the acute porphyruria for which no cause is known or demonstrable. It occurs in attacks lasting from a few days to several months, and usually terminating fatally in one of the attacks. Death, however, is thought to be due to some secondary cause in most instances (terminal infections). In a great many of the few cases reported nervous symptoms were present, particularly those of polyneuritis. The diagnosis is made by spectroscopic examination of the urine.

In the nine recorded necropsies the observations have been neither corresponding nor instructive. Two have shown some degree of liver degeneration, three positive signs of nephritis and in some of the others renal changes of minor importance. As to the nervous system, only once was degeneration of anterior horn cells found, and in some of the others no nervous lesion was demonstrable except degeneration of peripheral nerves.

A complete case report is given in the article. A brief but apparently complete bibliography is appended.

Emmet Bay.

The Glycolytic Power of the Blood. Y. Kawashima, Sc. Rep. Govt. Inst. Infect. Dis., Tokio **3**:193, 1924.

Red cells of the horse suspended in isotonic salt solution show a measurable oxygen absorption at 38 C. for twenty-four hours. This as well as glycolytic power is increased by the addition of phosphate mixture. Even more striking results are obtained with rabbit erythrocytes. In general oxygen consumption and glycolytic power run parallel. With whole blood the serum restrains the latter somewhat. Both disappear at the same time. In spite of their parallelism, the author regards them as essentially independent phenomena. The addition of sugar results in the longer preservation of the corpuscles, as well as in increased duration of the period of oxygen consumption.

The glycolytic power of red cells, lost on standing, is not restored by the addition of insulin. Likewise insulin exerts no effect on the glycolytic power of fresh cells. This glycolytic power must be viewed as being closely linked with their vital activity.

H. E. Eggers.

Microbiology and Parasitology

THE VIABILITY OF B. COLI AND B. AEROGENES IN SOIL. C. E. SKINNER and T. J. MURRAY, J. Infect. Dis. **38**:37, 1926.

The number of *B. coli* when added to a soil from feces or pure culture diminished until they disappeared. The number of *B. aerogenes* when added to a soil in pure culture or mixed with *B. coli* diminished almost as rapidly as did *B. coli*. *B. aerogenes* is found in many soils under natural conditions.

AUTHORS' SUMMARY.

THE EFFECT OF CLOSTRIDIUM HISTOLYTICUM ON THE TYROSINE IN PROTEINS. C. G. KING and LILLIAN V. HJORT, J. Infect. Dis. **38**:42, 1926.

A quantitative study was made of the tyrosine content of edestin, salmon, tuna, cheese, casein, milk, gluten, beef, cottage cheese and peptone before and after growth of *Clostridium histolyticum*. The relation of the digestive action of the organism to the formation of tyrosine crystals in the medium was noted. In seven of the ten mediums, destruction of tyrosine was found. In the remaining three cases there was practically no destruction of tyrosine during approximately three months' growth of the organism.

AUTHORS' SUMMARY.

MORPHOLOGIC VARIATIONS OF BACTERIA IN THE LAG PHASE. ARTHUR T. HENRICI, J. Infect. Dis. **38**:54, 1926.

The initiation of growth in a culture is accompanied by a morphologic transformation of the mature or resting cells to embryonic or growing cells.

From the evidence here presented it would seem that the lag phase as usually defined, i. e., the time from the moment of seeding until the maximum growth rate is attained, is composed of two parts: an initial dormant phase and a succeeding phase of accelerating growth during which apparently different factors are operative.

The period of dormancy is not entirely occupied by a transformation of the mature cells to the embryonic type. The curves for cell size may also show a lag phase, dependent on the age of the parent culture.

During the period of dormancy the cells may continue to change for a time in the same way that they would have had they remained in the parent culture. The degree which they do so varies with the size of the seeding, being greater with smaller seedings.

The inoculated cells show considerable variability in the rate at which they respond to the new environment by a morphologic transformation, as indicated by the increasing skewness in the frequency curves for size of cells during the accelerating growth phase. This variability probably explains the gradual acceleration in growth rate. In some cultures the frequency curves may show bimodality indicating a selection of a rapidly growing strain from the inoculum. The degree of skewness and tendency to bimodality varies with the size of the seeding, being greater with smaller seedings.

AUTHOR'S SUMMARY.

RELATIONS OF SURFACE TENSION TO BACTERIAL PHENOMENA. MARTIN FROBISHER, JR., J. Infect. Dis. **38**:66, 1926.

Surface tension is an important factor in bacterial growth, morphology, and probably in cell division, and to a less extent in the motility of bacteria, and their ability to retain Gram's stain.

Differences in ability to grow at low surface tensions offer a valuable and simple means of differentiation between species of bacteria. It is possible, by measuring the ability of organisms to grow at low surface tensions to distinguish *B. aerogenes* from *B. typhosus* and *B. morgani, B. diphtheriae* from *B. xerosis* and *B. hofmanni,* certain resistant types of streptococci from sensitive types, pneumococci from streptococci.

The serologic types of pneumococci do not differ from one another in their sensitiveness to low surface tensions. Low surface tension of the culture medium may be an important factor in determining the size of the individual cells, the rate and extent of cell division, and the cell grouping.

The growth-producing properties of Huntoon's "hormone" medium for pneumococci may be improved by raising the surface tension of the medium with charcoal.

When preparing medium for pneumococci, the surface tension should be raised to some point above 54 dynes.

The loss of virulence of pneumococci after treatment with surface tension reducents may be due to the fact that these bacteria disintegrate when they are subjected to low surface tension, and the dissolution of pneumococci by bile may be due to the low surface tension induced by this substance.

Sodium oleate was found to be the most useful reagent for reducing surface tension of culture mediums.

AUTHOR'S SUMMARY.

TUBERCULOSIS IN THE TROPICS. R. A. LAMBERT and B. FILHO, Am. Rev. Tuberc. **12**:173, 1925.

In 402 necropsy cases on unclaimed bodies from the Santa Casa de Misericordia Hospital in São Paulo, the author made the following observations in regard to tuberculosis: in 20.6 per cent tuberculosis was the cause of death or one of two stated causes; in 15.4 per cent active tuberculous lesions were found which, however, did not contribute materially to the death of the subject; in 4.5 per cent healed lesions only were present; in 32.3 per cent doubtful lesions, chiefly pleural adhesions, were seen. The percentage of lethal tuberculosis in negroes was 27.3 per cent, in white persons 15.5 per cent.

MAX PINNER.

TUBERCULOSIS IN FILIPINOS. G. R. CALLENDER and M. W. HALL, Am. Rev. Tuberc. **12**:273, 1925.

The study of 10,000 necropsy reports of the results of physical examination of large groups of population and the available statistical data lead to the conclusion that Filipinos have approximately two and a half times as much tuberculosis as Americans; that the natives of the Philippines, with the possible exception of the uncivilized tribes, are highly tuberculized, and that the high continuing mortality and morbidity are due to poor hygiene and inadequate sanitation.

MAX PINNER.

THE EFFECT OF SANOCRYSIN ON THE TUBERCLE BACILLUS IN VITRO. H. C. SWEANY and M. WASICK, Am. Rev. Tuberc. **12**:316, 1925.

Sanocrysin inhibits the growth of the tubercle bacillus in agar cultures, slightly in 1:1,000,000 dilution and markedly in 1:500,000 dilution. In bouillon cultures it inhibits growth slightly at 1:2,000,000 and completely at 1:1,000,000. When fresh rabbit blood agar is used as a medium, there appears to be a slight growth at first even in 1:50,000 dilution, but after 40 days growth becomes

arrested. There is no noticeable bactericidal effect in concentrations as low as 1:2,000 of sanocrysin for periods of two hours when about 5 billion bacilli are used, because good growth is obtained from these bacilli on Petroff's medium after the exposure. In a concentration of 1:5,000, approximately 100,000 tubercle bacilli, suspended in fresh human serum for periods as long as forty-eight hours, were able to produce tuberculosis in guinea-pigs only slightly more chronic and with less involvement than in control animals. Tuberculous lesions were produced in guinea-pigs from the bouillon cultures after three months' exposure in concentrations as low as 1:2,000 sanocrysin. There appears to be a reducing substance in living tubercle bacilli and some other gram-positive bacteria that is able to reduce metallic gold from sanocrysin, but this is not present in heat-killed bacilli. The gold is deposited first in the bacilli having granules, especially in the concentrations found in the body following injection of the salt.

MAX PINNER.

THE EFFECT OF INJECTIONS OF SANOCRYSIN ON NORMAL AND TUBERCOLOUS DOGS. K. L. MCCLUSKEY and L. EICHELBERGER, Am. Rev. Tuberc. **12**:329, 1925.

Sodium-auro-thio-sulphate (sanocrysin) is excreted principally by the kidneys over a period of approximately thirty days. The percentage of recovery of gold from the urine is practically 60 per cent. Albumin, varying in amounts from a trace to 1.2 Gm. per liter, was observed in all cases. The albuminuria increased with increased dosage, and lasted for a period of from four to ten days, with subsequent reappearance. The intravenous injection of the gold compound in the doses used in dogs caused diarrhea and oliguria, and seemed to affect the vomiting centers. The vomitus contained much bile but no gold. The excretion of urea, chlorides and creatinin in the urine was decreased following an intravenous injection of sanocrysin. From 3 to 5 per cent of gold was excreted through the intestine during the first week after injection. Intravenous injections of sanocrysin have no effect on body temperature. The greatest amount of gold from sanocrysin localized in the organs at any time does not exceed 32 per cent of the amount injected. Gold appears in the urine within thirty minutes after an intravenous injection of sanocrysin.

MAX PINNER.

THE QUESTION OF THE TRANSMUTATION OF TUBERCLE BACILLI AND PARATUBERCLE BACILLI. A. CALMETTE, Am. Rev. Tuberc. **12**:355, 1925.

Paratubercle bacilli are morphologically and tinctorially almost similar to tubercle bacilli, but they are less acid-fast and are markedly distinguished from the latter by a much smaller content of reducing sugars. They may produce lesions in warm blooded animals. Successive animal passage does not increase their virulence. Serologically they are closely related to tubercle bacilli. They are nontoxic for tuberculous animals. There is no conclusive evidence that they can be transformed into true tubercle bacilli. True tubercle bacilli can be made to lose all their tuberculogenic qualities and virulence, but they remain tubercle bacilli with an undiminished capacity of producing potent tuberculin and without alteration in their antigenic properties.

MAX PINNER.

THE ORIGIN OF THE TUBERCLE BACILLUS. S. J. MAHER, Am. Rev. Tuberc. **12**:365, 1925.

The author observed a patient with an abscess in the scrotum caused by smegma bacilli (no animal infection was done); the abscess healed promptly,

but the patient developed active tuberculosis within six months and died within a few weeks. The "smegma bacilli" from the abscess developed on artificial mediums into true virulent tubercle bacilli. On the strength of this observation and of a variety of circumstantial evidence of bacteriologic, immunologic and epidemiologic nature the author concludes that in nature there exist or can be artificially produced saprophytic varieties of Koch's bacillus, which can become virulent tubercle bacilli.

MAX PINNER.

OBSERVATIONS CONCERNING THE PECULIAR BEHAVIOR OF CERTAIN TUBERCLE BACILLI. W. M. STOCKWELL, Am. Rev. Tuberc. **12**:371, 1925.

If tubercle bacilli are rapidly transferred over a series of glycerol-free mediums, gram-negative, motile rods appear in the cultures, which produce varied forms of micro-organisms on different mediums. These gram-negative rods reverted to the acid-fast type when cultured on 15 per cent glycerol mediums. The gram-negative rods are apparently identical with Ferràn's alpha bacillus and represent one stage in the life cycle of the tubercle bacillus. They did not produce tuberculosis in animals.

MAX PINNER.

A CHEMICAL STUDY OF THE SPECIFIC ELEMENTS OF TUBERCULIN. J. HOWARD MUELLER, J. Exper. Med. **43**:1, 1925.

A CHEMICAL STUDY OF THE SPECIFIC ELEMENTS OF TUBERCULIN. II. THE PREPARATION OF RESIDUE ANTIGEN FROM OLD TUBERCULIN. J. HOWARD MUELLER, ibid. **43**:9, 1925.

The specific precipitin reaction and the skin reaction given by old tuberculin are attributable to two separate substances present in this material. The cause of the reaction first mentioned is a nonprotein. The cause of the skin reaction is probably but not surely a protein.

Methods which have been suggested for the standardization of tuberculin by precipitin or complement-fixation reactions should be revised.

A nonprotein gum has been isolated from broth filtrates of human tubercle bacilli grown on a simple medium. It fixes complement and precipitates in high dilution in the presence of homologous immune serum, but fails to give a skin test in tuberculous animals. The preparation and some of the chemical properties of the substance are described.

AUTHOR'S SUMMARY.

A STUDY OF HEMOLYTIC STREPTOCOCCI IN ACUTE RHEUMATIC FEVER, WITH AN ANALYSIS OF THE ANTIGENIC RELATIONSHIPS EXISTING AMONG CERTAIN STRAINS. CHRISTOPHER H. ANDREWS, CLIFFORD L. DERICK and HOMER F. SWIFT, J. Exper. Med. **43**:13, 1925.

Thirteen strains of hemolytic streptococci isolated from patients with acute rheumatic fever did not show any evidence of being related serologically.

Strains of hemolytic streptococci exist which, although identical by the agglutination test, do not show complete reciprocal agglutinin absorption. Serums prepared from such related strains may show some protective power in mice against another member of the group.

Some strains of hemolytic streptococci may absorb agglutinins from a serum prepared against another strain, and yet may fail to be agglutinated by that serum.

None of twenty strains of hemolytic streptococci isolated in New York City in 1924 and 1925, corresponded serologically with Dochez, Avery, and Lancefield's four type strains or with Gordon's type 1 strain.

AUTHORS' SUMMARY.

STUDIES ON THE BACTERIOPHAGE OF D'HERELLE. V. EFFECT OF ELECTROLYTES ON THE RATE OF INACTIVATION OF BACTERIOPHAGE BY ALCOHOL. JACQUES J. BRONFENBRENNER and CHARLES KORB, J. Exper. Med. **43**:71, 1925.

Addition of neutral salts to the lytic filtrate results in an increased rate of inactivation of the latter when alcohol is added to it. This effect of salts is the more marked the higher the valency of the cation. Conversely, removal by dialysis of salts originally present in the lytic filtrate tends to render lytic agents less sensitive to alcohol. Restitution of the original salt content to the dialyzed filtrate tends to bring the sensitiveness to alcohol in the dialyzed filtrate to the level of the nondialyzed control.

It appears, therefore, that inactivation of the lytic agent by alcohol depends directly on the rate of precipitation of the coagulable constituents of the medium, and is not the result of a direct toxic action of alcohol on "bacteriophagum intestinale." Considered in association with our earlier findings, these results speak in favor of the chemical nature of the agent of transmissible lysis.

AUTHORS' SUMMARY.

THE PRODUCTION OF PURPURA BY DERIVATIVES OF PNEUMOCOCCUS. I. GENERAL CONSIDERATIONS OF THE REACTION. LOUIS A. JULIANELLE and HOBART A. REIMANN, J. Exper. Med. **43**:87, 1925.

THE PRODUCTION OF PURPURA BY DERIVATIVES OF PNEUMOCOCCUS. II. THE EFFECT OF PNEUMOCOCCUS EXTRACT ON THE BLOOD PLATELETS AND CORPUSCLES. HOBART A. REIMANN and LOUIS A. JULIANELLE, ibid. **43**:97, 1925.

Pneumococcus extracts have been shown to be capable of producing hemorrhagic purpura in white mice, rabbits and guinea-pigs.

The purpura-producing principle resists heating to 100 C. for ten minutes; it resists oxidation; it is filter-passing; its activity is destroyed by digestion with trypsin; it is obtained from pneumococcus extracts by full saturation with ammonium sulphate after the acetic-acid-precipitable substances have been removed from the extracts.

The purpura-producing principle is common to all four types of pneumococcus, and apparently bears no relation to virulence.

The purpura-producing principle is probably a degradation product of pneumococcus.

This principle is not associated with the hemotoxin of pneumococcus, since the hemolytic activity of an extract may be destroyed without effect on the ability to cause purpura.

A study has been made of the variation in number of the blood platelets, and the red and white blood cells of white mice that have received injections with pneumococcus extract. The blood platelets were greatly diminished after the injection, the greatest decrease usually occurring after twenty-four hours. Purpuric lesions usually developed when the number of blood platelets became less than 500,000 per cubic millimeter. Regeneration of the platelets was

accomplished by the fourth to the ninth day, but there was an overregeneration, and the return to normal did not take place until two weeks had elapsed.

The red cells were also greatly reduced in number, but the rate of their destruction and regeneration was somewhat slower than that of the platelets. The leukocytes were slightly if at all influenced by the pneumococcus extract.

Pneumococcus extracts were shown to be thrombolytic and hemolytic. Heat destroyed the activity of both the lysins in vitro. Heated extract produced purpura in mice but did not cause a severe anemia. Extracts adsorbed with either blood platelets or red blood cells showed a marked diminution in their thrombolytic and hemolytic activity in vitro. Such extracts, however, produced purpura as well as severe anemia and thrombopenia in mice.

AUTHORS' SUMMARY.

THE RELATION OF BACILLUS ABORTUS FROM BOVINE SOURCES TO MALTA FEVER. THEOBALD SMITH, J. Exper. Med. **43**:207, 1926.

Comparative tests on guinea-pigs with *B. abortus* yield the best results when minute doses are injected subcutaneously and the animal is kept at least four weeks. *B. abortus* gradually loses its virulence for guinea-pigs under artificial cultivation. Two cultures resembling *B. abortus* from cattle, isolated from human cases of so-called Malta fever, are shown not to be identical with the bovine strains in their effect on guinea-pigs.

The results of studies of *B. abortus* from swine indicate a close relation between the porcine strains and the two human strains.

AUTHOR'S SUMMARY.

AGGLUTINATION AFFINITIES OF THE ABORTUS-MELITENSIS GROUP OF BACTERIA WITH SPECIAL REFERENCE TO TWO HUMAN STRAINS. MARION L. ORCUTT, J. Exper. Med. **43**:225, 1926.

The conclusions to be drawn from this study are that while there appears to be evidence of serologic distinctions between *B. abortus* and *B. melitensis* cultures as studied by earlier workers, the experiments reported in this paper show no serologic distinctions among the six strains used in the study. *B. melitensis* II and *B. melitensis* III were found to be identical with the bovine and swine strains by means of agglutination and agglutinin absorption reactions in unheated serums, by agglutination in heated serums, and by the use of heated cultures in unheated and heated serums.

AUTHOR'S SUMMARY.

NUCLEAR INCLUSIONS IN THE TESTICLES OF MONKEYS INJECTED WITH THE TISSUE OF HUMAN VARICELLA LESIONS. THOMAS M. RIVERS, J. Exper. Med. **43**:275, 1926.

Eosin-staining nuclear inclusions resembling those deemed characteristic of a certain well-known group of filtrable viruses, among which is varicella, were found in vervets' testicles inoculated with emulsified tissue of human varicella lesions.

AUTHOR'S SUMMARY.

BLASTOMYCOSIS OF THE LARYNX. CHEVALIER JACKSON, Arch. Otolaryng. **3**:99, 1926.

A case is described of primary blastomycosis of the larynx in which the histologic examination was made by B. C. Crowell and B. L. Crawford. The

photographs show typical blastomycotic lesions and organisms. This is a rare form of blastomycosis.

TRICHINOSIS. REPORT OF FOUR CASES, WITH RECOVERY, OCCURRING IN THE UNIVERSITY OF MICHIGAN STUDENT HEALTH SERVICE. W. L. BETTISON, J. A. M. A. **86**:609, 1926.

The infection in four cases of trichinosis occurring in university students was due to eating pork that was insufficiently cooked.

The edema of the face, especially of the eyelids and conjunctivae, was the most striking feature. This, together with the high fever, the almost general muscle stiffness and soreness and the eosinophilia, furnished sufficient evidence of trichinosis.

Absence of any early gastro-intestinal symptoms was noteworthy and quite important.

One case showed no elevation in the leukocyte count throughout the entire course of the disease.

In insufficiently cooked pork there is a constant menace of trichinosis.

The diagnosis of trichinosis was confirmed in the three of the four cases by microscopic examination of pieces of muscle removed from the gastrocnemius.

AUTHOR'S SUMMARY.

A NEW MEDIUM FOR GONOCOCCUS CULTURE. P. S. PELOUZE and L. E. VITERI, J. A. M. A. **86**:684, 1926.

The following medium is described as highly advantageous for first cultures and especially for subcultures of the gonococcus.

A calf's brain, weighing approximately 500 Gm., is forced through a wide-meshed gauze into 500 cc. of distilled water and placed in the icebox for twenty-four hours. It is then filtered several times through cotton of varying degrees of compactness. The resultant fluid is turbid, no matter how often it is filtered. To this is added 0.5 per cent of acid sodium phosphate and 1 per cent of peptone. It can now be autoclaved at 15 pounds' pressure for twenty minutes and kept as stock, or the final steps for its completion can be carried out.

To complete the medium, it is necessary simply to add one part of the brain bouillon to three parts of standard 2.5 per cent agar medium made from veal broth, with the addition of 0.5 per cent of sodium chloride and 1 per cent of peptone. It should then be adjusted to a p_H of 7.8, which allows for a reduction of two points in autoclaving, 7.6 being the desired end-point.

The medium is then tubed, autoclaved and slanted. After it solidifies, the usual cotton plug is replaced by a sterile rubber cork to retain the water of condensation, and the mediums keeps indefinitely.

When it is completed and cooled, some flocculation is present in the butt of the tube. This can easily be removed if the medium in bulk is placed in the autoclave, quickly brought to 15 pounds' pressure, removed, filtered, tubed and replaced in the autoclave for the completion of sterilization. While this improves its appearance, it seems to make some change in it which causes more scanty growths; consequently, we have not made use of it, preferring a good medium rather than a pretty one.

ON THE TRANSPLANTABILITY OF THE LARVA OF TENIA CRASSICOLLIS AND THE PROBABLE RÔLE OF THE LIVER IN CYSTICERCUS DISEASE OF RATS. F. D. BULLOCK and M. R. CURTIS, J. Cancer Res. **9**:444, 1925.

The experiments prove that *Cysticercus fasciolaris* can encyst and develop normally in the subcutaneous and probably also in the peritoneal tissues of the rat. This fact supports the theory that the rôle of the liver in cysticercus disease of rats is mechanical; that is, it probably acts as a filter through the pores (sinusoids) of which the tenia larvae cannot pass.

AUTHOR'S SUMMARY.

PRODUCTION OF AN EXPERIMENTAL SERUM FOR PREVENTION OF TYPHUS FEVER. C. NICOLLE and E. CONSEIL, Arch. de l'Inst. Pasteur de Tunis **14**:354-383, 1925.

Nicolle and Conseil have proved the protective power of human convalescent serum against typhus fever. Unfortunately, convalescent serum is not always easily procured. Monkeys and guinea-pigs have been found to be susceptible to thymus fever, but these animals are too small to be useful in supplying serum for human beings. Donkeys did not seem to be sensitive. Large doses (50 cc.) of virulent blood (monkeys and guinea-pigs used as controls presented the typical temperature curve) withdrawn from patients with severe typhus fever and injected intraperitoneally failed to cause the disease in donkeys. Recently, by using the intracerebral way and injecting 0.33 cc. of brain substance, taken on the second and third day of fever from guinea-pigs used for the passage of the virus, Nicolle and Conseil succeeded in producing typhus fever in donkeys. Intravenous injections of virulent brain substance, repeated at short intervals (3 x 6 cc., 4 x 6 cc.), may also be successful.

Typhus fever in donkeys is comparable to the disease in guinea-pigs; the blood of the donkeys seems to be less constantly virulent than that of the guinea-pigs; as in guinea-pigs, the Weil-Felix reaction is always negative. The serum of the donkeys that showed the typical reaction was found to have adequate protective power against typhus fever.

In general, the activity of the antibodies seems to be proportioned to the severity of the infection. Therefore Nicolle and Conseil suggest that the infection may be made more severe by repeating virulent injections at shorter intervals, by using the intracerebral or intravenous route or perhaps combining the two methods, by lowering the resistance of the animals through repeated bleedings or injections of other animal serum, toxic to donkeys; for a greater number of injections, repeated at longer intervals, does not seem to work out so well. One may believe that certain antiserums, as for instance the typhus fever antiserum, owe their activity to the infection caused by the first inoculation and not to the repetition of later injections. Therefore these serums are convalescent serums and different from antitoxic serums whose activity increases parallel to the amount of antigen inoculated.

P. BRUTSAERT.

CONVEYANCE OF PROPERTIES BETWEEN RACES AND SPECIES OF MICROBES. E. BURNET, Arch. de l'Inst. Pasteur de Tunis **14**:384-403, 1925.

Micrococcus paramelitensis, suspended in a 0.75 per cent salt solution, agglutinates when heated in a waterbath at about 80-90 C. while *Micrococcus melitensis* remains in a homogenous suspension. Among other species of

microbes tested, only *B. anthracis* (three strains of 3), *B. pestis* (eight strains of 8), *B. tyhosus* (two strains of 17) and *B. cholerae* (one strain of 6) showed a definite agglutination. This so-called thermo-agglutination does not occur in the absence of salt. It is accelerated by the acidification of the microbial suspension (2 drops of acetic acid to 10 cc. of suspension).

Micrococcus melitensis, when cultivated together with thermo-agglutinable *Micr. paramelitensis* (*M. melitensis* are put inside, the *M. paramelitensis* outside of a sack in collodion of following composition: alcohol 400 Gm., ether 600 Gm., nitric cotton 20 Gm.) and grown in broth during from three to five days (culture is indispensable — a short contact does not suffice) become as thermo-agglutinable as *Micr. paramelitensis.* The culture of *Micr. melitensis* in the presence of killed *Micr. paramelitensis* brings the same change. This is not only a modification of some physicochemical properties, but even a modification of the antigenic properties of the *Micr. melitensis* which are made more like those of *Micr. paramelitensis. Micr. paramelitensis* remains unchanged.

When cultivated in the presence of thermo-agglutinable strains of other species (*B. anthracis* or *B. pestis*) *Micr. melitensis* may also become thermo-agglutinable. Here, however, often two or three passages are required, and the antigenic properties are less modified.

Once acquired by such associated culture, the property of thermo-agglutinability is transmitted to the subcultures of the modified *Micr. melitensis.*

This phenomenon may be compared with other still incompletely known d'Herelle phenomena (transmissible lysis and the appearance of resistant cultures differing from the original susceptible cultures of the same strain in morphologic, cultural and serologic properties); also with some diseases in which a given tendency is imparted to the cells of an organism (tobacco mosaic, the chicken sarcoma of Peyton Rous).

P. Brutsaert.

Influences of Changes in Reaction of the Medium on the Activity of Bacteriophage. Alessandro Alessandrini, Ann. d'ig. **35**:1025, 1925.

It has been found by the author and others that bacteriophage activity is reduced or absent entirely in medium containing organic colloids such as gelatin, gum acacia, serum and ascites fluid. This is attributed to the changes in reaction which these substances undergo. D'Hérelle and others showed that activity takes place only within rather narrow limits, the optimum reaction being p_H 7 to p_H 8. The author found that these colloids, kept at 37 C., became more acid from day to day, as measured by titration with N/10 KOH. This "potential acidity" was greatest in gum acacia, then gelatin, blood serum, ascites fluid and least in plain broth and agar. He determined the degree of lysis by bacteriophage in the different mediums and found that it varied inversely with the potential acidity, so that it was greatest in the broth and agar, absent entirely in the gelatin and gum acacia. Further experiments are suggested to make clear the influence of acidity on bacteriophage activity.

B. R. Lovett.

Agranulocytic Infections. W. Rotter, Virchows Arch. f. path. Anat. **258**:17, 1925.

Rotter reports six cases of the condition which Schulz, who reported six cases, all in women, described in 1922 as "agranulocytosis." Since that date

the number of reported cases has rapidly increased. The condition, which occurs most frequently in women, is characterized by sudden fever, ulcerative inflammatory lesions of the buccal or pharyngeal cavities or of the vulva and vagina, absence of leukocytosis, relative lymphocytosis with almost complete absence of polymorphonuclear leukocytes, and only moderate anemia. The most striking feature is the absence of the leukocytes, the other blood elements being only slightly reduced. Four of Rotter's six cases occurred in females. The leukocyte counts varied from 600 to 2,300 in the individual cases. The polymorphonuclear neutrophil percentage was given as 0 in all cases but one, in which it was 24 per cent. Rotter paid especial attention to the histologic study of the bone marrow in his cases. The marrow was atrophic, showed no cellular reaction to the infectious process and contained no polymorphonuclear leukocytes and only a few myelocytes, the latter usually degenerated. The condition is interpreted as a lack of resistance to bacterial infection in individuals whose blood contains no granulocytes because of atrophy of the bone marrow.

O. T. SCHULTZ.

POST-TYPHOID OSTEOCHONDRITIS OF THE RIBS. V. J. OPPOKOFF and L. P. ODOJEWSKY, Virchows Arch. f. path. Anat. **258**:121, 1925.

The primary change in the post-typhoid involvement of the ribs is believed to be a nutritional, dystrophic disturbance similar in character to that which occurs in scurvy. Inflammation follows infection of such areas of lessened resistance. The entire costal cartilage is usually involved and the sixth to ninth cartilages, as a rule, are involved together.

O. T. SCHULTZ.

EXPERIMENTAL OSTEOMYELITIS. N. F. KATZENSTEIN, Virchows Arch. f. path. Anat. **258**:337, 1925.

Katzenstein made a histologic study of the bone marrow directly infected with staphylococci, using young and old rabbits in an attempt to explain the greater frequency of osteomyelitis in young individuals. Although differences were noted, they were not striking. In the early stage of the experimental local infection, the marrow of young animals becomes freed of leukocytes to a greater degree than is the case with older animals. In the succeeding stage of formation of leukocytes this process occurs diffusely throughout the marrow of all long bones in young animals but only locally in older animals. Giant cells appear earlier in the former than in the latter. The locally invaded marrow in all animals was more edematous than that involved by the hematogenous path.

O. T. SCHULTZ.

REACTIONS FOR THE SERUMLABILITY IN TUBERCULOSIS. M. v. LEMESIC and V. KOSANOVIĆ, Beitr. z. klin. Tuberk. **62**:277, 1925.

A comparison was made between the sedimentation rate of erythrocytes, Klausner's reaction, the silver nitrate reaction as advocated by Lange and Heuer, Matéfy's reaction and Dáranyi's reaction. They all indicate an active process. The sedimentation rate yields the most accurate results, Matéfy's reaction was most frequently positive in active cases (94 per cent), and the silver nitrate reaction was found to give acceptable results. The Klausner and Dáranyi reactions are not sensitive enough.

MAX PINNER.

TUBERCULOSIS AND INFLAMMATORY ACIDOSIS. H. SCHADE and F. CLAUSSEN, Beitr. z. klin. Tuberk. **62**:300, 1925.

Inflammatory processes increase the acidosis of the tissue juice. Pleural exudates have a p_H (at 18 C.) of 7.30—6.17, pus from cold abscesses 7.21—7.12, pus from tuberculous coxitis 7.02—6.79. The more acute the condition is the lower the p_H of its exudate. The optimal p_H for the growth of tubercle bacilli in artificial mediums coincides exactly with the p_H of acute exudates (6.00—6.50).

MAX PINNER.

THE CELLULAR REACTION AFTER THE INJECTION OF TUBERCLE BACILLI. N. L. JIWAGO and W. A. LUBARSKI, Ztschr. f. Tuberk. **43.**

After the injection of tubercle bacilli into the peritoneal cavity of white mice and tuberculous guinea-pigs (relatively immune animals) an exudate is formed which contains lymphocytes, polymorphonuclear leukocytes and macrophages (histiocytes). The leukocytes diminish soon after a rapid increase; the lymphocytes which appear at first in large numbers decrease slowly, and the histiocytes show a slow and permanent increase. Only a small percentage of tubercle bacilli are destroyed in the peritoneal cavity; most of them leave the cavity unchanged; a large number is enveloped by the histiocytes, some (in the guinea-pig) by the leukocytes.

MAX PINNER.

INVESTIGATIONS INTO THE TUBERCLE BACILLI ESPECIALLY ITS SEROLOGIC RELATIONS. FERD. WULFF, Acta path. et microbiol. Scandinav. **2**:149, 1925.

In addition to distinct differences in the conditions of growth, human, bovine and avian tubercle bacilli differ seriologically as determined by agglutination and agglutinin absorption.

STUDIES OF ACTINOMYCES FROM THE ORAL CAVITY. CARL NAESLUND, Acta path. et microbiol. Scandinav. **2**:110, 1925.

Actinomyces may occur in the mouth under normal conditions. The more or less strictly anaerobic forms appear to belong to the normal flora of the mouth, while the aerobic forms probably are only chance organisms that have entered the mouth from the outside. Experiments are under way to determine whether actinomycosis may be caused by ray fungi from the mouth.

AN EXPERIMENTAL STUDY ON THE PATHOLOGY OF THE BLACK-LEG. H. MORITA, Sc. Rep. Govt. Inst. Infect. Dis., Tokyo **3**:97, 1924.

The principal pathologic observations in experimentally induced black leg are are follows: (1) The principal change is in the skeletal muscles, with the subcutis and skin next in order. The former show cloudy swelling, later waxy degeneration and final myolysis with pseudo-eosinophilic infiltration. (2) The cutaneous edema is mainly of toxic origin, in part of inflammatory character. (3) Rancid odor is not in evidence. (4) Gas formation occurs only to the point of microscopic appearance. The foamy appearance is a postmortem or agonal process. (5) The causative organism is transferred through the lymph channels. (6) To the extent that the organisms are found in the blood stream they are there as a result of passive transmission rather than as a phase of actual septicemia. (7) A significant and constant finding is the appearance of hemorrhage in the suprarenal cortex, and partial loss of chromaffinity in the medulla.

H. E. EGGERS.

Immunology

INTRACUTANEOUS TESTS WITH HUMAN AND WITH BOVINE TUBERCULIN. HAROLD F. DOWNING and HAROLD L. HIGGINS, Am. J. Dis. Child. **31**:178, 1926.

Both bovine and human tuberculin should be employed in routine tuberculin tests, not only to determine the diagnosis of the type of tubercle bacilli present, but also to increase the value of the test by detecting cases which would otherwise be missed. In this series, the missed cases would have amounted to 15 per cent of the total tuberculous patients.

Evidence from two cases tends to confirm earlier reports that in the first stages of tuberculosis the patient will react to but one type of tuberculin, presumably that of the infecting type, while later the patient reacts to other types (group reaction).

AUTHORS' SUMMARY.

STUDIES ON THE PROTECTIVE SUBSTANCE IN ANTIPNEUMOCOCCUS SERUM. LLOYD D. FELTON, Bull. Johns Hopkins Hosp. **38**:33, 1926.

The amount of precipitate in antipneumococcus serum by dilution with water is much greater than in normal serum. In antipneumococcus serum the zone of maximal precipitation is to the alkaline side of that in normal serum. The protective effect of antipneumococcus serum does not run parallel with the amount of precipitate. For further details the original article must be consulted.

A SEROLOGIC RELATIONSHIP OF TYPE-SPECIFIC AND DEGRADED PNEUMOCOCCI. HOBART A. REIMANN, J. Exper. Med. **43**:107, 1925.

Immune serums prepared with the degraded or variant forms of pneumococci (R strains) are similar in their reactions to serums prepared with the protein or cell solutions of pneumococci. They contain antibodies reactive with the protein of all types of pneumococci, but no antibodies reactive with the type-specific substances.

Pneumococci of the variant or R form, regardless of type derivation, are serologically identical and have the antigenic characteristics of pneumococcus protein. They evoke the species-specific and not the type-specific antibodies.

Antipneumococcus serums obtained by immunization with S. strains may contain species-specific antibodies in addition to those which are type-specific. Each kind of antibody can be removed separately from these serums by selective absorption with the R or S strains of pneumococci.

AUTHOR'S SUMMARY.

ON THE SURFACE COMPOSITION OF NORMAL AND SENSITIZED MAMMALIAN BLOOD CELLS. STUART MUDD and EMILY B. H. MUDD, J. Exper. Med. **43**:127, 1925.

The interfacial tension method has been applied to the study of the surface composition of mammalian blood cells and to certain other particles.

Unsensitized erythrocytes and stromata possess only a small margin of stability in the interface and pass readily into the oil phase. Specifically sensitized erythrocytes and stromata possess much greater stability in the interface and pass into the oil only with considerable mechanical aid; characteristic deformations of the erythrocyte surface or the interface or both often result.

With special immune serums prepared by Landsteiner and van der Scheer the quantitative relations are such as to indicate that the increased polarity

of the sensitized erythrocyte surface is due to combination of the red cell surface lipoids with hemolytic sensitizer. These results are corroborative of the conclusion of Landsteiner and van der Scheer that erythrocytes contain specific lipoid-soluble antigens.

The tentative conclusion is reached that with these antihorse-erythrocyte serums at least the agglutinins combine predominantly with the protein of the red cell surfaces.

Fresh human leukocytes are spread and disintegrated by the interfacial stresses. After heat injury over the condenser with substage lamp the leukocytes typically do not enter the boundary surface. They are pushed before the advancing interface and, if their further advance is obstructed, bend the interface backward to form peninsulas and vacuoles. This change after heating is in the opposite sense to that to be expected from denaturation of the proteins of the protoplasm.

Fresh oxalated rabbit platelets pass easily into the oils. After heating over the substage lamp these elements also become less oil-miscible.

The interfacial tension relations of blood cells, bacteria, and several cell products are tabulated.

AUTHORS' SUMMARY.

THE IMMUNITY PRODUCED BY THE GROWTH OF TETANUS BACILLI IN THE DIGESTIVE TRACT. CARL TENBROECK and JOHANNES H. BAUER, J. Exper. Med. **43**:361, 1926.

A method for the production of tetanus by the injection of a fixed number of spores is described, together with the tests made in selecting animals for experimental work.

Guinea-pigs fed a single serologic type of tetanus bacilli will, after six months, show considerable amounts of antitoxin in their serums and will manifest immunity to the type fed. To other types they are just as susceptible as are controls.

Animals fed several types are immunized to each of these types. It is pointed out in the discussion that the digestive tract of man may carry several types and that he probably reacts in a manner resembling the guinea-pig carriers.

Guinea-pigs that carry tetanus bacilli and have antitoxin in their serums show little if any resistance to tetanus toxin.

As there is no relation between the amount of antitoxin in the blood and immunity to tetanus, we believe that other bodies, specific for type, must occur and make for the immunity observed.

AUTHORS' SUMMARY.

THE PRECIPITIN REACTION IN THE STUDY OF ANIMAL RELATIONSHIPS. ALAN ARTHUR BOYDEN, Biol. Bull. **50**:73, 1926.

The precipitin reaction has been used in the study of animal relationships since 1900 with somewhat inconsistent results. An attempt was therefore made: (1) to improve the technic of the reaction, and (2) to apply an improved technic with a known range of error to the study of animal relationships.

The technic employed was as follows: 1. The ring test or contact method was used throughout because of its sharp end-point. 2. Antigen dilutions were made only in buffered salt solution of known p_H. 3. A double series of antigen dilutions was used thus decreasing by one-half the usual interval between successive tubes and giving a more accurate result. 4. All antigen solutions

employed were standardized by determining their protein content with a modified Kjeldahl process.

With this technic, together with a statement of the error in reading the reaction, the results obtained in medicolegal tests would be somewhat more certain. Furthermore, the results obtained by all those who use the precipitin reaction for any purpose would become strictly comparable and therefore of greater value.

The technic described, with a maximum error of plus or minus one tube or 50 per cent in terms of titer, was applied to the study of the relationships of sheep, goat, beef, pig, horse, dog, human and various rodent blood. The results obtained showed essential agreement with themselves and with the results of Nuttall's quantitative studies. The precipitin reaction seems therefore quite suitable for the study of animal relationships. In fact, it is particularly well fitted for such studies because its results can be expressed in quantitative terms and are therefore independent of interpretation.

AUTHOR'S ABSTRACT.

PROCESSES TO INCREASE THE PRODUCTION OF ANTITOXINS. G. RAMON, Ann. de l'Inst. Pasteur **40**:1, 1926.

Ramon has found that the titer of diphtheria and tetanus antitoxins is much higher in horses immunized with anatoxin or toxin which is administered simultaneously and in the same region with a powdered tapioca. This starch causes the organism to modify with more ease and intensity the antigen and then to use it for the elaboration of antitoxin.

G. B. RHODES.

ON THE HYPERSENSITIVITY TO TUBERCULOSIS AND TO KOCH'S BACILLUS IN EXPERIMENTAL TUBERCULOSIS. A. BOQUET and L. NYRE, Ann. de l'Inst. Pasteur **40**:11, 1926.

Immunity and hypersensitivity are two distinct and independent states of the tuberculous organism. The opinion that variations in tuberculous allergy at various stages of an infection should be interpreted as indicating variations of general immunity and therefore of a high prognostic value, should be revised. Numerous experiments are cited showing the multiple aspects of the reactional relations. There may be manifested a hypersensitivity following inoculations with any strain of the tubercle bacillus, virulent or nonvirulent or with a killed organism or its extracts, but these nonvirulent or killed organisms do not confer immunity. Tuberculous sensitivity precedes resistance to reinfection.

G. B. RHODES.

INFLUENCE OF SPECIFIC IMMUNE SERUMS ON CULTURES OF PATHOGENIC MICRO-ORGANISMS. M. NICOLLE and E. CESARI, Ann. de l'Inst. Pasteur **40**:43, 1926.

There is a greater numerical increase in cultures of many pathogens when grown in specific antiserum than when grown in normal serum. The specific antiserum may cause the adhesion of substances in the serum to the micro-organism which are favorable to its nutrition, or it is possible that the specific serum contains products of the disintegration of the antigen that are particularly favorable to the alimentation of the corresponding organism. A coagulated antidiphtheritic serum does not form a better selective medium than normal coagulated serum.

G. B. RHODES.

EXPERIMENTAL RESEARCH ON HEMOLYSIS. HECTOR DIACONO, Arch. de l'Inst. Pasteur de Tunis **14**:449, 1925.

Domingo reported recently (*Compt. rend. de la Soc. de biol.* **98**, p. 1933) that rabbits that have previously received repeated injections of washed sheep cells, give a notable increase of the hemolytic properties of their serum following an intravenous injection of heterologous albumin. In the case of one prepared rabbit, twelve hours after one injection of milk (3 cc.), the hemolytic titer was increased from 1:600 to 1:1,100; however, the latter titer was not constant.

Diacono used antisheep guinea-pig serum for the Wassermann reaction (modified technic of Rubinstein) and wished to determine whether by a single subcutaneous, intravenous or intracardiac injection of milk he could increase the antibody content of the serum in his previously prepared guinea-pigs. The results were negative.

At the suggestion of Remlinger and Bel, Diacono substituted uncrushed barley and grass for bran and grass in the feeding of guinea-pigs used for the production of antisheep hemolysin. Since that time he has had a continuous series of unsuccessful efforts in that all serums have had but one-half the strength of those previously obtained. By stopping the use of barley and replacing bran and grass, and without giving more injections of sheep cells, the serums of the animals regained their normal average hemolytic activity.

P. BRUTSAERT.

IMMUNIZATION REACTIONS IN ASPERGILLOSIS. A. CORPACI, Bol. d. Ist. sieroterapico Milanese **4**:295, 1925.

The serum of dogs and guinea-pigs receiving injections with spores or threads of aspergillus contained specific complement-fixing substances. Extracting the spores with ether before injection gave stronger results. Precipitins or agglutinins were not obtained.

IMMUNIZATION PROPERTIES IN AVITAMINOSIS AND IN STARVATION. G. PARRINO and P. LEPANTO, Bol. d. Ist. sieroterapico Milanese **4**:319, 1925.

Starvation and avitaminosis lead in guinea-pigs and pigeons to loss of weight, lowering of the temperature and reduction of the normal and artificially evoked immune properties. In addition, in starving guinea-pigs there is an increase in the neutrophil polymorphonuclear leukocytes, while in avitaminosis there is lymphocytosis. In guinea-pigs both conditions are accompanied by a pseudo-eosinophilia. Avitaminosis causes more marked changes than starvation.

THE DANGERS OF ANAPHYLAXIS IN SEROTHERAPY AND A METHOD OF AVERTING THEM. B. VERNONI, Bol. d. Ist. sieroterapico Milanese **4**:353, 1925.

The dangers of anaphylaxis from injections of therapeutic serums under various conditions are discussed.

THE PRESERVATION OF SYPHILITIC ANTIBODIES. W. GAEHTGENS, Centralbl. f. Bakteriol. I. O. **96**:119, 1925.

The addition of antiseptics preserves the syphilitic antibodies in serums better than drying. Linen, cotton and silk are better to dry the serum on than filter paper, asbestos or quartz, but only two thirds of the serums remained active for two months on them. Glycerol preserves the antibodies for four weeks in 100 per cent. of cases, but the number decreases after that period.

Chloroform acts the same as glycerol. In serums preserved with glycerol or chloroform, inhibiting substances which are thermolabile develop after a time. For the Sachs-Georgi reaction also, antiseptics are preferable to drying. Glycerol seems to be the best medium for preserving syphilitic antibodies for a long time.

B. R. LOVETT.

THE FORMATION OF HETEROGENEOUS ANTIBODIES IN ANIMALS OF THE GUINEA-PIG TYPE. K. A. FRIEDE, Centralbl. f. Bakteriol. I. O. **96**:136, 1925.

In immunizing guinea-pigs and dogs with hen's erythrocytes which contain heterogeneous antigens for sheep and turtle erythrocytes, no heterogeneous antibodies for sheep and turtle erythrocytes were found. The author concludes that in immune serums of animals of the guinea-pig type, which have received injections with erythrocytes or organs containing heterogeneous antigens, no heterogeneous antibodies are demonstrable.

CONCERNING THE MULTIPLICITY OF HETEROGENEOUS ANTIGENS IN ANIMAL CELLS. K. A. FRIEDE, Centralbl. f. Bakteriol. I. O. **96**:154, 1925.

In the organs and nucleated erythrocytes of animals of the guinea-pig type there exist, besides species-specific antigens, biochemical complexes that are common to these and to animals of other species — heterogeneous antigens. The following heterogeneous antigens have been demonstrated: Turtle erythrocytes contain heterogeneous sheep and hen antigens. Hen erythrocytes contain heterogeneous sheep and turtle antigens. Sheep erythrocytes contain heterogeneous hen and turtle antigens. Organs of animals of the guinea-pig type contain, besides heterogeneous sheep antigen, the species-specific heterogeneous antigen of turtle and hen. Heterogeneous agglutinins for erythrocytes of sheep, turtles, and hens could not be demonstrated.

B. R. LOVETT.

INCUBATION PERIOD IN PASSIVE ANAPHYLAXIS. E. FRIEDBERGER and S. SEIDENBERG, Klin. Wchnschr. **4**:1823, 1925.

Immediate passive sensitization of guinea-pigs was obtained by injection of the serum of sensitized guinea-pigs. The incubation period after passive sensitization with serum from rabbits is regarded as due to the nonspecific inhibiting action of foreign serum.

TWO DIFFERENT TYPES OF PHENOMENON IN THE SPECIFIC ANTIGEN-ANTIBODY REACTION OF MONOGENETIC ANTIPROTEIN SERUMS WITH THE HOMOLOGOUS ANTIGENS IN VITRO. E. FRIEDBERGER and T. IKEDA, Klin. Wchnschr. **4**:2149, 1925.

A double ring is formed whenever a highly potent antiprotein serum is covered with the homologous antigen, providing the antigen is added with sufficient care to prevent any mixing at the interphase. The lower ring consists of material heavier than the antiserum and tends to sink. It contains the isogenetic precipitate, contains no material staining with sudan III or osmic acid and shows complement binding. The upper ring is of material of lower density than the diluted antigen and diffuses upward. It contains the heterogenetic precipitate and is in large part ether soluble. Diphtheria toxin and antitoxin give only a single ring, corresponding to this upper one.

ARTHUR LOCKE.

HISTOGENIC IMMUNITY IN ANTHRAX. I. KRITSCHEWSKY and A. BRUSSIN, Arb. a. d. Microbiol. Inst. d. Volksunterrichtskomissariats **1**:352, 1924.

Following intraperitoneal injection of anthrax bacilli into the guinea-pig and intravenous injection into the rabbit, there regularly occurs a fatal septicemia, despite precautions which rigidly exclude the possibility of cutaneous infection. Hence the skin cannot be regarded as the sole portal of entry, as is assumed by Besredka.

H. E. EGGERS.

STANDARDIZING OF THE WASSERMANN REACTION. OLUF THOMSEN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **44**:192, 1925.

A method of standardization of the Wassermann reaction is described based on three principles: (1) the determination of the smallest amount of the patient's serum that gives a positive reaction, (2) the determination of the smallest amount of lipoid extract or (3) of the number of units of complement which can be bound by a fixed amount of serum and antigen. Variation in a single individual can be followed quantitatively and expressed in the form of a curve. Differential diagnosis is possible between syphilis, leprosy, frambesia and other tropical diseases.

JEAN OLIVER.

RESEARCH CONCERNING COMPLEMENT FIXATION IN TUBERCULOSIS. II. RELATIONSHIP BETWEEN ANTIGEN AND ACID-FAST SAPROPHYTES AND THE SERUM OF A TUBERCULOUS GUINEA-PIG. TOYO OGAWA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **44**:218, 1925.

This is a continuation of earlier work which showed that various acid-fast bacilli (butter, smegma, timothy bacilli, etc.) if defatted completely gave a fixation of complement with the serum of tuberculous persons. Butter and smegma bacilli gave in some cases as great a fixation as tubercle bacilli.

In the present article the work is continued using the serum of tuberculous rabbits. The reactions varied considerably with the various types of bacilli and with the manner in which they were defatted. The addition of lecithin did not regularly increase the degree of the reaction. There was a certain parallelism between the course of the infection and the strength of the reaction. The author believes that these results indicate that constituents of the acid-fast saprophytes and the tubercle bacilli differ more quantitatively than qualitatively.

JEAN OLIVER.

MEINICKE'S TURBIDITY REACTION IN SANATORIUM WORK. O. EICKE, Ztschr. f. Tuberk. **44**:218, 1926.

This reaction is as specific as the Wassermann reaction, and in latent syphilis more sensitive (*692* cases).

MAX PINNER.

THE TYPING OF PNEUMOCOCCI BY AGGLUTINATION. TORU TAKAMI, Tohoku J. Exper. Med. **6**:260, 1925.

Several Japanese investigators were unable to confirm the subdivision of pneumococci into four groups by means of agglutination reactions. Each strain was agglutinated only by homologous serum. The author found that, after growth on artificial medium, the strains were all different, but that after

passage through an animal they could be divided into the four groups. He concludes that in typing pneumococci by agglutination, one must use strains made virulent by animal passage or strains isolated directly from the body, not strains that have been grown on artificial medium.

B. R. LOVETT.

Tumors

PRIMARY LUNG TUMORS IN MICE FOLLOWING THE CUTANEOUS APPLICATION OF COAL TAR. JAMES B. MURPHY and ERNEST STURM, J. Exper. Med. **42**:693, 1925.

The external application of tar to a number of separated areas on the surface of mice, in such fashion that no single area is irritated sufficiently long to cause lesions of the skin, has resulted in a very high incidence of lung tumors. This incidence ranged from 60 per cent. in one experiment to 78.3 per cent. in another. Control mice from the same stock but from 3 to 6 months older, and for that reason the more liable to spontaneous lung tumors, failed to show a single instance of such growths. Even in a stock in which spontaneous lung tumors had been frequent, the incidence for corresponding age periods has never been above 5.5 per cent., while the average has been between 1 and 2 per cent. over a period of years. The tumors in the tar-painted animals occur as small white nodules, either single or multiple. They are typical epithelial neoplasms, identical histologically with those described by previous authors as occurring spontaneously in mice.

Some possible factors in the causation of the tumors are discussed briefly.

AUTHORS' SUMMARY.

STUDIES ON THE RELATION BETWEEN TUMOR SUSCEPTIBILITY AND HEREDITY. II. THE INCIDENCE OF TAR TUMORS IN STRAINS OF MICE HAVING A DIFFERING INCIDENCE OF SPONTANEOUS GROWTHS. CLARA J. LYNCH, J. Exper. Med. **42**:829, 1925.

Two strains of mice, one with a high, the other with a comparatively low, incidence of spontaneous tumors of the mammary gland, when painted between the shoulders with coal tar extract developed tar tumors with about practically identical frequency. In each series twenty mice were used, selected from two stocks with differing cancer incidence and apparently without definite records as to cancer heredity.

FIBROSARCOMA OF THE THYROID. I. T. ZECKWER, Arch. Surg. **12**:561, 1926.

A search through the literature revealed only six cases which Zeckwer considered true sarcomas of the thyroid. Other cases were inadequately described and were confused with rapidly growing tumors of epithelial origin. The case reported is one in which extensive metastases to the lung had occurred from an infiltrating growth of the thyroid, and the microscopic picture presented dense, disorderly arranged fusiform and spindle shaped cells with fibrillar formation.

N. ENZER.

HAS MORTALITY FROM CANCER CHANGED IN COPENHAGEN? P. HEIBERG, J. Hyg. **24**:291, 1925.

The main result accruing from Heiberg's investigations is that during the twenty years in which the newest, and consequently the best, Copenhagen

material was available, the number of deaths from cancer of the stomach in relation to the population in the age class 55 to 64 years proved to be exactly the same from year to year.

TYPES OF CYSTICERCUS TUMORS. F. D. BULLOCK and M. R. CURTIS, J. Cancer Res. **9**:425, 1925.

The large group of tumors induced in a single organ, the rat liver, by a single agent, *Cysticercus fasciolaris* [the larva of cat tapeworm, *Tenia crassicollis*], shows a wide variation in morphology. Tumors of different histologic structure occur not only in different individuals but often in different cysts in the same animal and even in different parts of the same cyst. However, all of the cysticercus tumors so far observed have been of mesoblastic origin. Apparently the liver cells are either not stimulated to neoplastic proliferation by this agent or are protected from it by the interposed cyst wall.

AUTHOR'S SUMMARY.

VARYING DEGREES OF MALIGNANCY IN CANCER OF THE BREAST. ROBERT B. GREENOUGH, J. Cancer. Res. **9**:453, 1926.

The degree of malignancy of a given case of cancer of the breast can be determined with reasonable accuracy by study of the histology of the original tumor; and three classes — low, medium, and high malignancy — can be distinguished. Such a classification is of importance in prognosis, and should be of assistance in estimating the value of therapeutic measures.

In estimating the degree of malignancy of a given tumor, the following factors are of importance: degree of differentiation, as shown by arrangement of cells around an open gland lumen (adenocarcinoma); degree of secretory activity of cell protoplasm, as shown by vacuoles and droplets of mucoid material; uniformity of size of cells and of nuclei, as opposed to variations in size; absence or presence of hyperchromatic changes in nucleus, and few or many mitotic figures, and whether irregular or not.

High malignancy is shown by cells and nuclei of irregular shape and size without secretory function, and arranged in solid columns, large or small, together with numerous and irregular mitoses and hyperchromatism. The extreme degree of these features is pleomorphism.

A tumor of adenomatous arrangement (adenocarcinoma) with uniform sized cells and nuclei, few mitoses, and absence of hyperchromatism, indicates low malignancy. A high degree of round cell infiltration appears to indicate a considerable degree of cell degeneration, and is not to be relied on as an indication of the resistance of the individual to the cancer growth.

Hyalinization of the stroma does not indicate active resistance to the tumor growth, but is rather a factor of the age or previous condition of the mammary tissue in which the tumor lies.

AUTHOR'S SUMMARY.

CONCERNING "MALIGNANT THYMOMA"; WITH A REPORT ON A CASE OF PRIMARY CARCINOMA OF THE THYMUS. N. C. FOOT, Am. J. Path. **2**:33, 1926.

The following characteristics point to the origin of a tumor from the thymus:

The growth is found in the anterior mediastinum at the site of the thymus and is firm and not very lobulated.

It does not tend to invade bone, extending down the sternum without involving it. The tumors reported by Symmers and Vance and by Jacobson both invaded vertebrae, and constitute exceptions to this rule.

The pleura and pericardium are involved by direct extension, rather than by metastasis, and the lung may also be directly invaded.

There is a general resemblance of the type cells to those of the embryonic or postembryonic thymus, and the presence of structures resembling Hassal's corpuscles, while helpful, is not essential to diagnosis.

The sarcomatous tumors occur in children or young adults, the carcinomatous in patients of "cancer age," in later life.

Metastasis below the diaphragm is rare, being reported in only three cases: that of Ambrosini, in Symmers and Vance's second case and in the case described by Friedländer and Foot.

A case is described in a man, aged 45, in which there was a marked production of Hassal's bodies; the tumor invaded the superior cava and gave rise to metastasis in the lungs and adjacent lymph nodes.

PRIMARY GELATINOUS CYLINDRICAL CELL CARCINOMA OF THE LUNG. WILHELM HUEPER, Am. J. Path. **2**:81, 1926.

The tumor is regarded as having started from the alveolar epithelium. It is pointed out that the presence of acid-fast bacilli in the sputum in gangrenous conditions in the lung due to carcinoma sometimes may lead to a wrong diagnosis of tuberculosis.

ON A GROWTH-PROMOTING FACTOR IN TUMOUR TISSUE. H. CHAMBERS and G. M. SCOTT, Brit. J. Exper. Path. **7**:33, 1926.

A substance is produced from tumor cells during autolysis which in vivo causes an appreciable increase in the rate of tumor growth. The substance is formed under conditions which preclude its being a living agent. It is a fairly stable chemical body which is apparently derived from the nuclear structures.

S. A. LEVINSON.

MULTIPLE MYELOMA OF SKULL. I. PENTMAN, Virchows Arch. f. path. Anat. **258**:161, 1925.

Pentman reports a case of multiple myeloma which he considers unusual because the tumors were limited to the skull.

O. T. SCHULTZ.

SQUAMOUS-CELL CARCINOMA OF GALLBLADDER. T. AWOKI, Virchows Arch. f. path. Anat. **258**:276, 1925.

Awoki reports a case of keratinizing epithelioma of the gallbladder, of which condition he could find thirty-three examples in the literature. He believes that his tumor arose, not by direct metaplasia from indifferent cells, but by indirect metaplasia of normal cylindrical epithelium which had become dedifferentiated during regeneration.

O. T. SCHULTZ.

GRANULOSA-CELL CARCINOMAS OF THE OVARY. H. O. NEUMANN, Virchows Arch. f. path. Anat. **258**:284, 1925.

Neumann describes in detail six carcinomas of the ovary which he believes originated from follicular granulosa cells. In two of his tumors the follicular character of the growth was marked, being associated with the formation of atypical ovum-like bodies. In the remaining neoplasms the tissue was mainly of the cylindroid, medullary type, and only occasional follicle-like structures

could be seen. Neumann concludes that these tumors, which are also termed folliculomas, cannot arise from normal ripe follicular epithelium but must come from indifferent cells which have not entered into the formation of follicles.

O. T. SCHULTZ.

NEURINOMA OF STOMACH AND MAMMA. S. L. EHRLICH and G. L. DERMAN, Virchows Arch. f. path. Anat. **258**:405, 1925.

Ehrlich and Derman report a tumor of the stomach and one of the mammary gland composed of cellular and fibrillated tissue with the bandlike and rosette-like arrangement of elongated nuclei which Verocay has considered characteristic of neurinoma. The mammary tumor was so cellular as to be considered malignant. Because of the histologic morphology of their tumors, the authors believe that they were derived from the sheath of Schwann cells of nerves and that they were neurinomas.

O. T. SCHULTZ.

FOOD AND GROWTH OF CANCER. F. LUDWIG, Ztschr. f. Krebsforsch. **23**:2, 1926.

Ludwig fed sixty mice with a diet free from vitamins for twelve days before and after inoculation of carcinoma. The inoculation did not take in any of them. The vitamin-free food had no effect when given after the appearance of carcinoma. The results were similar, although not so perfect (35.7 per cent protection), in fourteen rats inoculated with a sarcoma after fifty to sixty days of a diet free from vitamins.

Medicolegal Pathology

CARBON MONOXIDE POISONING. GRADUAL CUMULATIVE EFFECTS IN YOUNG CHILDREN, WITH REPORT OF A FATAL CASE. A. M. STEVENS, J. A. M. A. **86**: 1201, 1926.

There is a seasonal increase, in the winter, of the hazard of gas poisoning, acute and chronic.

There is a cumulative poisonous effect of repeated or continuous exposure to small amounts of carbon monoxide.

Young children and infants are peculiarly susceptible to gradual carbon monoxide poisoning.

In serious cases of gradual gas poisoning, there will probably be more than 10 per cent of carbon monoxide in the blood.

There is a simple and rapid qualitative test for carbon monoxide in the blood, which will show the presence of 10 per cent or more. [Three drops of suspected blood are dropped into 5 c c. of water and shaken so that a pink solution forms. For control, three drops of a normal person are shaken up in the same way. To both tubes are added a drop of 5 per cent. solution of sodium hydroxide. If the suspected blood remains a clear pink while the control solution turns a dirty green, it means the presence of carbon monoxide in the suspected blood of at least 10 per cent.]

Clinicians should be on the alert to recognize cases of gradual poisoning by carbon monoxide, especially in infants.

AUTHOR'S SUMMARY.

IDENTIFICATION OF FIREARMS AND PROJECTILES. SYDNEY SMITH, Brit. M. J. **1**:8 (Jan. 2) 1926.

When an automatic pistol is fired, the empty case is automatically thrown out of the chamber and a new cartridge slides forward into its place. The

empty case when examined with a low power microscope presents certain surface cuts or scratches caused by irregularities in the breech or in the slide. These cuts may be absolutely characteristic and imprinted on every cartridge, and when found may prove that the cartridge case was used in a certain weapon. The firing pin may also leave a mark on each shell, aiding in the identification of the weapon in which it was exploded. On every bullet fired from a pistol or revolver there will be certain marks. The most prominent of these consist of a series of grooves, sloping either to the right or left, which are caused by the lands in the barrel of the weapon. Weapons of the same manufacture will have the same number of grooves, direction, width and pitch. Some projectiles having a slightly smaller diameter than usual for that particular weapon will frequently fail to show "rifling."

Bullets removed at necropsy are frequently so distorted as to fail to give characteristic markings.

WILLIAM D. MCNALLY.

OBSERVATION OF A METHOD USED IN CRIMINAL ABORTION. W. DEROME, Ann. de méd. légale **5**:314, 1925.

Distention with air under pressure which escaped with a noise when the uterus was opened, with characteristic features of air embolism in the lungs, together with discovery of the instruments used, led Derome, professor of legal medicine in the University of Montreal, to conclude that an attempt had been made to bring about abortion by injecting air into the uterus.

The fetus of about 2½ to 3 months' gestation and amniotic sac were intact, and the sac had plugged the outlet so that the air had not escaped. The os contained bloody mucus, and the placenta was wounded. Death was sudden, and the body was still warm when examined.

This observation is of interest in view of insufflation of the tubes with air, and the injection of air by way of the tubes to produce pneumoperitoneum, measures advocated and employed therapeutically or as aids to diagnosis.

E. R. LE COUNT.

PRESSURE OF THE CEREBROSPINAL FLUID IN BULLET WOUNDS OF THE HEAD AND BRAIN. R. JUDE and R. PIÉDELIÉVRE, Ann. de méd. légale **5**:411, 1925.

In an effort to explain the abruptness with which death may follow bullet wounds of the head, measurements were taken of the pressure of the spinal fluid in the lumbar region in dogs first anesthetized and then shot.

It was found that the instrument used was not of a scope sufficient to measure the increase in pressure which followed a few seconds after shooting; it exceeded 100 after oscillating about at lower levels. The withdrawal of 20 cm. of the fluid several times in some animals was followed in each instance by registrations of pressure as high as the manometer would record.

Starting with the assumption that increased hydraulic pressure by the fluid in the ventricles on the important centers about and in the brain stem and medulla caused by entrance of gas and projectiles into the cranium was a large factor in causing death, they were forced to conclude that the increased pressure was due to a number of causes, among which sudden large hemorrhage within the cranium was probably the most important.

It was also learned that the cerebrospinal fluid possesses extreme mobility and that variations in pressure are easily obtained by changes of the body to prone, vertical or other positions and even by marked extension or flexion of the head on the trunk.

E. R. LE COUNT.

TETANUS AFTER CRIMINAL ABORTION. G. H. SCHNEIDER, Med. Klin. **22**:134, 1926.

Two deaths from tetanus after criminal abortion are reported. Of 111 cases collected from the literature, death occurred in 91 per cent.

DEATH DUE TO AN ACCIDENT SUSTAINED FIFTEEN YEARS PREVIOUSLY. R. HANSER, Frankf. Ztschr. f. Path. **33**:188, 1925.

Following a brief introductory discussion of the difficulty of establishing a causal relation between death and injury, when a considerable period of time has elapsed between the two, in cases other than those in which cord injuries are followed by urinary difficulties and chronic urosepsis, Hanser reports a case in which he considered death to have been the result of an accident sustained fifteen years previously. The purpose of the postmortem examination was to establish the validity of a claim for compensation. The accident, which occurred in 1909, consisted of a fall from the third to the second floor of a building in which the victim was working as a mason. The immediate diagnosis was contusion of the pelvis; there was no evidence of fracture. Following the accident the man was never free from neuralgic pains in the pelvic region; he was incapable of carrying on his work, although able to walk with the aid of a cane; progressive postural deformity developed. In 1923, there occurred a low intestinal obstruction of three weeks' duration. An indurated area in which stenosis was occurring could be felt in the rectum 10 cm. above the anus. The diagnosis was inoperable carcinoma; an artificial anus was made in August, 1923, following which there was slight improvement. Death occurred in June, 1924, and was ascribed to carcinoma of the rectum and ascites. The postmortem examination, after exhumation of the body to establish the widow's claim for compensation, revealed marked stenosis of the rectum, but the wall and mucosa were free from tumor. The narrowing was due to a mass of tissue which surrounded the rectum and filled the left half of the pelvis, making its way through the left obturator foramen into the upper part of the thigh. The inner surface of the left iliac bone was roughened by inflammatory exostoses; no evidence of previous fracture could be seen. Microscopic examination of the mass showed it to be composed of dense inflammatory tissue, which was necrotic in places. Hanser concluded that the entire course of the man's illness, including the terminal stenosis of the rectum which resulted in death, was the result of a chronic inflammatory process which originated in the accident. He considered the claim for compensation valid.

O. T. SCHULTZ.

Technical

A COLORIMETRIC METHOD FOR THE DETERMINATION OF THE p_H OF CEREBROSPINAL FLUID. I. MCQUARRIE and A. T. SHOHL, J. Biol. Chem. **66**:367, 1925.

A comparison of blood and cerebrospinal fluid shows that the two normally have the same p_H 7.35 to 7.40, $\pm$ 0.02.

ARTHUR LOCKE.

THE DETERMINATION OF GASES IN BLOOD AND OTHER SOLUTIONS BY VACUUM EXTRACTION AND MANOMETRIC MEASUREMENT. III. GASOMETRIC DETERMINATION OF METHEMOGLOBIN. D. D. VAN SLYKE, J. Biol. Chem. **66**:409, 1925.

The carbon dioxide combining power of blood which has been reduced with ammoniacal hydrosulphite is compared with that of unreduced blood. The methemoglobin content is proportional to the increased carbon dioxide combining power of the reduced sample.

ARTHUR LOCKE.

THE DETERMINATION OF CALCIUM IN TISSUES, FECES, AND MILK. R. C. CORLEY and W. DENIS, J. Biol. Chem. **66**:601, 1925.

The samples are prepared for analysis by a two hour autoclaving at 180 C. with 0.1 N sodium hydroxide, instead of by the usual ashing procedure.

ARTHUR LOCKE.

IRON IN NUTRITION. II. QUANTITATIVE METHODS FOR THE DETERMINATION OF IRON IN BIOLOGICAL MATERIALS. C. A. ELVEHJEM and E. B. HART, J. Biol. Chem. **67**:43, 1926.

A new method is proposed for the determination of iron in materials, such as milk, which are low in iron and high in phosphorus content.

ARTHUR LOCKE.

A MICRO METHOD FOR THE DETERMINATION OF BASE IN BLOOD AND SERUM AND OTHER BIOLOGICAL MATERIALS. W. C. STADIE and E. C. ROSS, J. Biol. Chem. **65**:735, 1925.

This micro method is for the determination of total base in biologic materials. The bases are converted to sulphates and are precipitated by the addition of benzidine hydrochloride. Excessive quantities of phosphates must be removed previous to the titration. The analytic error is approximately 1 per cent.

ARTHUR LOCKE.

ACTUAL TEMPERATURES ATTAINED BY MEDIUMS IN AUTOCLAVE STERILIZATION. ANNE BENTON and ALAN LEIGHTON, J. Infect. Dis. **37**:353 (Oct.) 1925.

Sterilization should be controlled according to temperature, not pressure. Autoclaves should be equipped with reliable thermometers and should have the air outlet at the bottom.

In sterilizing any substance which is easily injured by heat, much time can be saved and injury avoided by disposing the material in small containers spaced to permit free access of steam to their surfaces.

AUTHORS' SUMMARY.

LUMBAR PUNCTURE AND PREVENTION OF POSTPUNCTURE HEADACHE. H. M. GREENE, J. A. M. A. **86**:391, 1926.

It is recommended that a small round neeedle be used and that the patient remain as quiet as possible during the puncture in order to reduce to a minimum leakage of arachnoid fluid, and thus prevent headache.

THE SPECIFIC DIAGNOSIS OF ECHINOCOCCUS DISEASE. G. DEUSCH, Deutsch. med. Wchnschr. **51**:1319, 1925.

Deusch states that the intracutaneous injection of hydatid fluid is the most reliable means in the diagnosis of echinococcus infections, and much more dependable than the complement-fixation reaction. The reaction remains positive, however, for a long time after the surgical removal of the cysts.

MICROSEDIMETRY. O. GRAGERT, Klin. Wchnschr. **4**:2436, 1925.

The microdetermination of erythrocyte sedimentation introduced by Linzenmeier and Raunert is accompanied by greater sources of error and difficulty than the macromethod but gives comparable values and is more rapid.

ARTHUR LOCKE.

Society Transactions

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, March 8, 1926

RUTH TUNNICLIFF, M.D., *President, in the Chair*

SOME MISCONCEPTIONS REGARDING THE RELATION OF HEREDITY TO CANCER AND OTHER DISEASES. STUDIES IN THE INCIDENCE AND INHERITABILITY OF SPONTANEOUS CANCER IN MICE. MAUD SLYE. (From the Otho S. A. Sprague Memorial Institute and the University of Chicago.)

A serious handicap is met in the effort to make known the facts of heredity and their relation to disease and to therapeutic measures. This handicap consists in what may well be called fundamentalism in the scientific field; that is, preconceived ideas and prejudices not based on scientific research but on general impression, hearsay evidence and the like, handed on from one to another and thus established in general opinion.

Scientific terms, frequently misunderstood and misused by clinicians and research workers, form a strong background of entrenchment to prejudice and preconceived opinion. For example, great confusion attends the use of such terms as eugenics, congenital and hereditary. "Congenital" and "hereditary" are frequently used as if they were synonymous.

A congenital disease is contracted in utero. Any disease which is hereditary is not so contracted, but instead is the result of characters derived from ancestral germ plasma, inherent in the ovary and the sperm cell. By the right kind of experimentation, hereditary diseases can be proved not to have been contracted in utero. Characters which are hereditary can be carried through many generations before their frank emergence. Such behavior of any character takes it wholly outside the realm of the congenital and proves it hereditary.

Although the inheritability of disease types is of great interest both to the medical and to the lay mind, it is striking how few adequate studies have been attempted regarding the relation of heredity to any pathologic condition. In the absence of any such studies, it is equally striking how generally an "opinion" is held on the subject of heredity in connection with any given type of disease.

I desire strongly to reemphasize the misleading nature of such extempore "opinions" on the subject of heredity, since heredity is a profoundly determining factor in the nature and behavior of any disease, and pronouncements on the subject should be based only on intensive heredity studies.

Thus the most serious obstacle in establishing the facts and influence of heredity is the general misconception of the nature of heredity itself, and of the type of test which is adequate to prove the inheritability or noninheritability of any disease.

The method of statisticians in attempting to settle the question of the inheritability of any disease, is to take such records as they can get of the two parents, or of the four grandparents, and on such inadequate data they decide questions of heredity. But it is easily possible that in the third genera-

tion there should appear a character shown by neither parent nor any one of the four grandparents.

For example: pigmentation is "dominant" over albinism. If, therefore, we mate two black mice, one of which is purebreeding black and one of which is hybrid black (that is, carries albinism potentially), we shall get only black mice in their immediate offspring. One-half of these will be purebreeding black and one-half will be hybrid black, and nothing in their external appearance indicates which are dominant black and which are hybrid black. If then we select for both parents of the next generation, hybrid black individuals from such a cross, we shall get some albino mice in their immediate offspring.

Here, then, are albino mice readily obtained by the classic method, from ancestry which showed no white in either parent or any one of the four grandparents. By mating two of these whites, we shall immediately get a 100 per cent albino strain which will remain 100 per cent albino, unless pigmentation is again hybridized in. Thus by one mating of two recessive albinos, derived from hybrid black, is a strain which had apparently been 100 per cent black immediately converted in this branch into 100 per cent white.

In exactly the same way a 100 per cent blue-eyed family can be secured by mating two recessive blue-eyed individuals obtained in the third generation from hybrid brown-eyed parents.

Again, since cancer susceptibility is recessive to cancer resistance, it is possible to get in the third generation cancerous individuals when neither parent nor any one of the four grandparents was cancerous, but when each parent was hybrid noncancerous, while one of each pair of grandparents was hybrid noncancerous, the other in each pair being dominant noncancerous.

Thus by the classic method, cancerous individuals are readily obtained when neither parent nor any one of the four grandparents was cancerous.

By the continued mating of hybrid black with dominant black, or of hybrid noncancer with purebreeding noncancer, recessive albinism and recessive cancer susceptibility can be held off for any number of generations desired. Such characters have frequently been held off in this laboratory for twenty-five or more generations. As long as one parent is purebreeding black or purebreeding noncancerous, no albinism or no cancer susceptibility will occur in the strain. As long as one parent is hybrid black, hybrid noncancerous, albinism or cancer susceptibility will be carried potentially in the strain. When eventually two hybrid blacks or two hybrid noncancerous individuals are mated, the recessive character, albinism, or cancer susceptibility will occur in some of the immediate offspring. This accounts for the sudden appearance of cancer in human families when there has been no known cancer for two or more generations.

When these facts are grasped the absurdity of attempting to settle questions of heredity by the statistical method is at once apparent, since the statistician can never discover which of the parents were purebreeding and which were hybrid cancer resistant. Only by the experimental method of selective breeding and analysis with the right number and the right kind of crosses can the question of the inheritability of any disease be settled.

Opponents of the fact of the inheritability of cancer have used the experimental production of cancer as their chief argument against it. But the facts of the experimental production of cancer thus far obtained are all consistent with the inheritability of cancer. For example, the inheritance behavior of grafted cancer proves normal regeneration to be dominant over abnormal regeneration, just as does the inheritance behavior of spontaneous cancer.

Experimentally produced tumors like those of Fibiger's work with so-called "spiroptera cancer," or the work of Bullock and Curtis with liver sarcomas

induced by feeding rats with tapeworm larvae, have shown that such tumors are produced only in susceptible members of susceptible strains.

The outcome of the study of tar cancers cannot yet be foreseen since so many of these studies are still under way, but whatever the outcome may be, it cannot decide the question of the inheritability of cancer, since there is not and cannot be any complete biologic control in the field of heredity in such studies.

No one can deny the inheritability of the tendency to grow hair, yet continued painting with coal tar destroys the hair growing mechanism. Coal tar painting undoubtedly can, in the same way, destroy the cancer resistant mechanism.

Another type of obstacle in establishing the facts of cancer heredity is the idea voiced in the annual propaganda of the Society for Cancer Control. This argument is in substance that since we cannot study the inheritability of human cancer, because we cannot control human matings, the demonstrated facts of cancer heredity do not apply to the human species, and can be discarded. In no other field of scientific endeavor do we assume that because we cannot as yet make a given test of a demonstrated scientific fact it is not a fact. We do not discard the conclusions of higher mathematics and higher physics because they are complicated and difficult.

If we would establish permanent recorded periodic examinations of each living individual, and permanent recorded accurate necropsy findings of all dead, in three generations we would have valuable scientific data. These data would undoubtedly include matings of double cancerous parentage, matings of double noncancerous parentage, matings of noncancerous with hybrid carriers, and matings of cancerous with hybrid carriers. These are exactly the matings by which we test the inheritability of cancer in short lived animals. Such records, if accurately taken and correctly interpreted, would furnish an equally exact test for the human species.

Another strong obstacle in the way of establishing a clear comprehension of the relation of heredity to cancer is the announcement of what are designated as strains carrying a permanently fixed percentage of cancer; as, for example, the recent work of Lynch of the Rockefeller Institute, and Bagg of Cornell Medical College, and the older work of Loeb of Washington University.

Each of these workers assumed as the sole basis of his experimentation, a fixed percentage of cancer in the strains used. In each case the attempt was to discover whether a given type of experimentation would increase the incidence of cancer in a strain supposed to produce only a given exact percentage of cancer when not experimented on. Thus the experimentors hoped to prove whether or not certain types of irritation or traumas were potent in the causation of cancer.

Every strain which is producing some cancerous and some noncancerous individuals, no matter how low or how high the percentage of cancer, is a strain hybrid to cancer. Such a strain is made up of some cancerous members, some dominant noncancerous and some hybrid noncancerous members, and nothing in the external appearance will distinguish the dominant noncancerous from the hybrid noncancerous. There is therefore no certainty which of these might develop cancer without experimentation, as the cancer potentiality of every member of such a strain is wholly dependent on what matings are made. Any experiment of this kind using unanalyzed members of a hybrid strain might select the very members that would develop cancer irrespective of the experimentation, and such a possibility should be ruled out by complete biologic control.

While the results of experiments of this type have no bearing on the inheritability of cancer, the fact of the inheritability of cancer has a marked influence on the results of such experiments, and this fact should be considered in arranging the details of control.

There is a scientific method of procedure for those who cannot accept the demonstrated fact of the inheritability of cancer and the evolutionary evidence for its application to man. This scientific procedure consists not in categorically denying facts that cannot be disproved and that have indisputably been found true by many workers, but rather to begin the measures which inevitably must produce scientific data for the investigation of heredity in man.

A new era in medical research and in the practice of medicine will begin when the intricate and universally present influence of heredity is recognized and made use of in the study of diseases and of reactions to all therapeutic measures.

THE NATURE OF THE ACTIVE PRINCIPLE IN TUBERCULIN. ESMOND R. LONG and FLORENCE B. SEIBERT.

Tuberculin may be defined as a preparation obtained from the tubercle bacillus, which elicits a specific inflammatory response in tuberculous animals, but is nontoxic for normal animals. Many different kinds of tuberculins are available, which presumably owe their activity to an active substance common to all.

The nature of this active substance has been frequently but not exhaustively investigated. The problem is a fundamental one, not only for its bearing on tuberculosis, but also for its bearing on other chronic infections. Presumably such reactions as the luetin, mallein and abortin reactions are identical in character, and the agent responsible for the reaction of hypersensitiveness belongs to the same chemical fraction of the infecting micro-organism in each case.

Argument has rested chiefly on the question whether the active principle of tuberculin is a protein or not. To aid in the solution of this problem we have carried out the following experiments: Tuberculin was prepared in large quantity from a medium of the following composition: asparagin 5, ammonium citrate 5, potassium acid phosphate 3, sodium carbonate (dry) 3, sodium chloride 2, magnesium sulphate 1, ferric ammonium citrate 0.05, glycerol 50 and water 1,000. The tubercle bacillus grows luxuriantly on this medium, yielding a highly potent tuberculin which invariably contains protein.

The activity of preparations made from the growth of tubercle bacilli appears to be due to a colloidal substance, for as a rule on prolonged dialysis no active substance passes through the dialyzing sac, even when all the salts, color, odoriferous substance, glycerol and other constituents of the original medium have dialyzed out. Occasionally small amounts of active substance appear to diffuse, particularly after much chemical manipulation of the material.

The methods of protein precipitation throw active substance out of solution. Acetic acid precipitates a protein which is active, maximum precipitation occurring at p_H 4. Precipitation is not complete, however. The filtrate still contains protein and still has tuberculin activity. Trichloracetic acid precipitates protein more nearly completely; however, traces of protein and at the same time of active substance remain in solution. Saturation with ammonium sulphate precipitates at the same time all of the protein and all of the active principle.

On hydrolysis of tuberculin, whether by enzymes or by acid, activity remains as long as protein of the type classed as whole protein is present. We have selected precipitation by trichloracetic acid as an arbitrary measure for whole protein. As protein decreases and proteose increases in enzymic digestion, activity decreases. When proteose alone is destroyed by erepsin, the activity of the preparation is not affected. The protein which can be precipitated by trichloracetic acid from tuberculin exposed to mild acid hydrolysis is highly active, but a small amount of activity persists in the proteose fraction after the removal of the trichloracetic acid precipitate.

From these experiments it seems probable that the activity of tuberculin is associated primarily with a protein molecule, but persists in spite of a certain amount of disintegration of the molecule.

MUTATION FORMS OF THE TUBERCLE BACILLUS. HENRY C. SWEANY.

In experiments by Sweany and Wasick (*Am. Rev. Tuberc.* **12**:316 [Dec.] 1925) on the effect of sanocrysin on the tubercle bacillus in vitro, it was observed that following the exposure of ordinary cultures of tubercle bacilli to various concentrations of the preparation there appeared rapidly growing forms which at first were thought to be contaminations; but after finding them in every culture, a complete study was made to determine their relationship to the tubercle bacillus. Culturally, they vary a great deal, but belong chiefly in the salmonella group of bacteria. In guinea-pigs, rabbits and rats they produce changes resembling the early lesions of tuberculosis in calves described by Calmette (quoted by Bushnell: A Study in the Epidemiology of Tuberculosis, New York, 1922). The first reaction is a diffuse inflammation and edema at the site of inoculation, then a diffuse hepatitis followed by a localization in the gallbladder and an accumulation of yellow, granular bile containing the bacilli. The duodenum next is involved and sometimes ulcerates. The inflammation extends into the intestines and often kills the animal by an enteritis. If not, the infection spreads along the lymph glands to the lungs, sometimes causing a terminal pneumonia. If the animal survives this stage, the spleen enlarges, and at the end of eight to ten days contains tubercle-like abscesses that have a necrotic center and a peripheral zone of epithelioid cells. Grossly, these abscesses have a flat, white appearance instead of the pearly luster of tubercles.

These tubercle-like structures do not always occur. They were produced only by strains obtained from rather avirulent bacilli exposed to 1:2,000 concentration of sanocrysin for seventy days. The other animals died from a more acute condition. These results indicate that sanocrysin does not kill tubercle bacilli quickly, and that the compound seems to stimulate mutation —effects to be considered in the use of the drug in patients.

Extensive observations on the granular forms of the tubercle bacillus permit the following conclusions. The granule is primarily a resting stage caused by a change of environment or old age which does not permit perfect metabolism of the acid-fast rod, although some may be degeneration forms. The normal young bacillus with a waxy coat of variable thickness and consistency has a rather diffuse gram-staining portion which agglomerates as the bacillus ages or the environment changes, until one, two, three or many granules form within the capsule. Many of these granules are uniform or oblong, in the center of the bacillus, while others occupy either one end, both ends or three or more places along the body. Careful examination demonstrates that these granules have one, two, three or more nuclei. There is no relation between the acid-

fastness and the ability to stain by the Gram method. The granules studied in the fresh vegetative form have been caused to sprout into new bacilli by elongation or pulling apart leaving "end caps," by budding to form two unequal end caps, by pulling apart in several sections to create a beaded bacillus, and by sprouting singly or in pairs. Coccoid forms also occur in certain avirulent or low grade strains exposed to an unfavorable environment for a long period. These coccoid forms under more favorable circumstances appear to lengthen out into the classical bacilli. These forms perhaps represent part of what Spengler called "splitter." The other part are those true degeneration forms of acid-fast rods. At first they form zooglear masses that may or may not be acid-fast; finally, true short bacilli may form if the environment is suitable.

The size of these granules is variable and the pathogenicity varies, as is evidenced by experiments on Berkefeld filtrates containing them. Some produce a septicemia and acute condition resulting in death; others cause a peculiar glandular enlargement, while others produce changes more like the classical type of tuberculosis. Microscopically, some of these granules are barely visible. In unfavorable environment the coccoid forms may grow out into diplococci, tetrads and staphylococcus forms—some of these cultures assuming peculiar pigmented hues, mucoid and waxy consistency and other interesting characteristics.

PATHOLOGICAL SOCIETY OF PHILADELPHIA

Regular Meeting, March 11, 1926

J. H. AUSTIN, M.D., *Presiding*

STAINING OF ANIMAL FATS IN TISSUE BY CAROTIN. FRED D. WEIDMAN.

The observation that some of the cases of "jaundice" in children were referable to a heavy carrot diet prompted the thought that carotin might be turned to account for laboratory purposes.

The material was prepared by extracting the fats from ground, dried carrots with three changes of hot alcohol, concentrating the extractive by distillation, followed by saponification of the fats by solid potassium hydroxide. The product was extracted several times with ether, the ether extract washed several times with water and finally evaporated to a red-brown thick, oily residue. The yield was very small—only 3 cc. from half a bushel of carrots. There was a marked difference in the product, depending on the variety of carrot employed; the large, coarse, darker red specimens yielding a correspondingly deeper red oil. It was soluble only up to 2 per cent in 85 per cent alcohol and very sparingly in 70 per cent.

For staining histologic sections (frozen) an 85 per cent alcoholic solution was prepared and applied in the same way as with sudan III. The fat became stained in twenty minutes. The larger fat globules of subcutaneous tissue stained orange—carotin was satisfactory to this extent, but the more minute globules within sweat glands appeared so faintly yellow that there would be room for doubt in cases of undetermined fatty nature. The same would doubtless obtain in pathologic fatty degenerations.

Subcutaneous fat was stained orange when the skin was kept immersed in the solution in the gross over night.

For intravitam purposes, the concentrated carotin was made into the colloid emulsion of Dewey; 45 cc. of this opaque, yellowish, milky material was injected into the ear vein of a rabbit. The animal died in three days, showing an intense serous inflammation of all the great serous cavities, together with numerous miliary splotches of fatty infiltration over the liver. Neither the abdominal nor subconjunctival fats were discolored.

A white mouse received 2 cc. of the emulsion subperitoneally. At necropsy, twenty-four hours later, the abdominal fat was but slightly more yellow than normal. In the test tube it was found that our carotin behaved toward oleic acid, paraffin oil and oil of bergamot in the same way that sudan III did, i. e., there was absorption of the dye by all of the fats.

Alcoholic solutions keep well in diffuse daylight, but one of the lots became bleached in two weeks.

I can thus confirm Hess and Myers that, although carotin may occur in the blood (in quantities sufficient to discolor the plasma), it may not affect the skin. I believe, however, that this is referable to the low staining index of carotin and not because the carotin was unable to pass the capillary endothelium (in contrast with bile pigments). The situation is quite different from jaundice, because bile pigments stain the protein constituent of the skin as carotin does not. A number of different factors thus enter into the problem of carotinoid skins, among which are to be counted the plasma concentration of the pigment, and particularly the thickness of the skin proper. The latter factor is important in explaining the higher incidence of pigmentation in infants.

Conclusions.—The carotin yield from carrots is so small that it does not promise well for practical use as a dye. Carotin is available as a fat dye for histologic purposes, but is far inferior to sudan III and scharlach R. It does not differentiate between the important animal fats. It does not promise well as an intravitam stain for fat on account of its low staining index.

DIAPHRAGMATIC HERNIA IN A NEW-BORN INFANT. RALPH M. TYSON.

The subject was a white male infant, born after a rapid labor, and appearing in every respect normal for six days. On the seventh day after birth, the child became dyspneic and cyanosed while being nursed. Physical signs and roentgen-ray examination pointed to the presence in the left pleural cavity of coils of intestines. The infant went into collapse and died nineteen hours after the onset.

At necropsy the entire duodenum, jejunum, ascending and transverse colon were found in the left pleural cavity. The latter communicated with the abdominal cavity by an opening in the left diaphragm measuring 1.5 by 2 cm. and having regular edges. The opening, apparently a congenital fault, was situated laterally and posteriorly near the origin of the diaphragm, and was entirely distinct from the rings through which the vena cava, esophagus and aorta pass.

The displaced intestines showed evidence of early gangrene.

A HUGE OVARIAN CYST IN A GIRL OF 13. THOMAS FITZ-HUGH, JR.

The specimen was removed at operation from a white girl, aged 13 years and 4 months. She had noted enlargement of the abdomen three months previously, the enlargement increasing rapidly. Menses were normal.

Physical examination showed a tall, well developed girl who was somewhat pallid, weak and dyspneic. The temperature was 99.4; the pulse rate, 92. Additional positive findings were a high diaphragm, costal breathing, some

engorgement of the superficial thoracic veins, moderately impaired resonance in the left supracardiac area, and a huge tense abdomen of the general contour of full term pregnancy. A fluid wave was demonstrable in the abdomen.

Diagnostic abdominal paracentesis revealed thick mucinous material which would hardly flow from the needle. At operation, 17 pints of this material were removed before the cyst could be delivered. Following extirpation of the cyst, the patient made an uneventful recovery, all abnormal physical signs disappearing.

The cyst measured 39 by 24 by 13.5 cm. The fallopian tube with its fimbriated extremity was flattened out on the surface of the specimen. The cyst was multilocular, and its contents varied in consistency from thin gelatinous to thick gelatinous, and from clear transparent to opaque amber.

Histologic examination revealed no evidence of malignancy.

STUDIES OF A CASE OF HEMOLYTIC ICTERUS. EDWARD ROSE.

The patient, M. R., a white girl aged 19, was admitted to the University Hospital, Dec. 4, 1925, with a history of jaundice of varying degrees for four years, punctuated by attacks of vomiting, increasing weakness and occasional pain in the left flank. Examination revealed generalized icterus, a marked enlargement of the spleen and slight enlargement of the liver. Splenectomy was performed on January 7, after which the jaundice rapidly disappeared, and she left the hospital, improved, February 7. There was no history to suggest the existence of similar disease in other members of her family.

Before operation, the hemoglobin content varied from 60 to 68 per cent, erythrocytes from 3,050,000 to 3,985,000, leukocytes from 7,400 to 9,700, with a rather high polymorphonuclear percentage, platelets from 124,000 to 236,000, and skin cells from none to 14 per cent. Fragility tests showed partial hemolysis in as high as 0.6 per cent sodium chloride, and complete in 0.4 per cent; studies with solutions of varying p_H showed hemolysis to occur in much more alkaline solutions than normal. There was no evidence of hemolytic action of the patient's serum on her own cells or on normal cells of the same type (IV). The Van den Bergh test showed a direct delayed positive, and the indirect of 12.8 units. The bile pigment in the serum could not be dialyzed through a collodion sac. The urobilin output in the feces varied from 7,500 to 11,500 units a day.

At operation blood was obtained from the splenic artery and vein. Platelet counts made at operation showed a difference between the arterial and venous blood well within the limits of error. The Van den Bergh test showed no perceptible difference between the two samples (positive delayed direct; indirect 13 units). Fragility tests showed no difference, and spectrophotometric examination of serum from the artery and vein showed no difference in bilirubin content. Cultures made from the freshly removed spleen were negative. The spleen was much enlarged (11 by 13 by 8 cm., and weighing 1,719 Gm.) and intensely engorged, soft, with a smooth, slightly thickened capsule pitted by a few scars. The cut surface was homogeneous and engorged, and the follicles could not be distinguished. Histologic examination showed localized increases in capsular thickness, looseness of splenic architecture, small compact follicles, disintegration of erythrocytes, engorgement and swelling of the endothelial elements.

Twenty-five days after operation, the direct Van den Bergh reaction was negative, the indirect 0.3 units. The fragility of the red cells remained increased, although not markedly, beginning hemolysis being noted at 0.55 per cent sodium chloride, and complete at 0.4 per cent. The hemoglobin

had risen to 85 per cent twenty-five days after operation, the red cells to 4,160,000, and the leukocytes were 9,600, with a relative increase in lymphocytes. The urobilin output in the feces fourteen days after operation had dropped to 1,400 units a day. The percentage of reticulated red cells had dropped to 0.5 to 2 per cent before discharge.

An observation of some interest was the demonstration that fresh red cells from the patient which had been exposed to the action of an extract made from her spleen at operation (by grinding with salt solution) showed greater fragility than cells exposed to her splenic artery hemoglobin and to normal salt solution for equal periods of time. Such hemolytic power may of course reside in any spleen or any tissue.

THE APEX THE MOST ACTIVE PART OF THE LUNG. JOSEPH WALSH.

Macroscopic and microscopic study of the normal adult human lung shows a progressive decrease in size of alveoli from apex to base, whereas in newborn infants, alveoli are uniform in size throughout the lung. These observations are taken to mean that respiratory movements are greatest in the apex and gradually decrease toward the base. The commonly accepted view that in the apex respiratory movements are relatively slight, is held to be incorrect.

That the apex is the portion of the lung most seriously involved in tuberculosis is due to its great excursion during respiration, since it is well known that activity of a part favors extension of the tuberculous process, whereas rest favors its healing.

Book Reviews

INTESTINAL TUBERCULOSIS. ITS IMPORTANCE, DIAGNOSIS AND TREATMENT: A STUDY OF THE SECONDARY ULCERATIVE TYPE. By LAWRASON BROWN, M.D., Chairman of the Medical Board of the Trudeau Sanatorium, Saranac Lake, New York, and HOMER L. SAMPSON, Roentgenographer of the Trudeau Sanatorium, Saranac Lake, New York. Cloth. Price, $4. Pp. 304, with 112 illustrations. Philadelphia: Lea & Febiger, 1926.

This is a thorough discussion of the subject; more than that, it carries a significant message, based on the author's rich experience. Intestinal tuberculosis is not a terminal and hopeless complication of pulmonary tuberculosis, yielding to no therapeutic efforts, as generally represented in textbooks; if diagnosed early, it is as amenable to treatment as an incipient or moderately advanced pulmonary tuberculosis. An extensive statistical presentation of symptoms and signs renews forcibly the impression of the protean character of the disease and of the impossibility of a correct diagnosis. But the authors make the assertion, well substantiated by their statistics, that a correct observation of certain filling defects after a radio-opaque meal or enema and definite alterations in the motility of the intestines make it possible to diagnose ulcerations correctly in approximately 100 per cent. In the chapter on pathologic anatomy (which is all too brief) it is pointed out that Gardner found much tendency to spontaneous healing, rendered futile, as a rule, by the simultaneous spread of the disease. But in patients who had been treated a considerable length of time, complete healing had occurred with epithelial regeneration. The treatment consists of heliotherapy or, in Saranac Lake, preferably irradiation with the mercury vapor quartz lamp. Since heavy dosage of rays is given over the entire surface of the body, it is surprising that no mention is made of the effect on the pulmonary process. It has frequently been the experience, here and in Europe, that certain pulmonary processes react so severely to ray treatment as to make a thorough heliotherapy of a concomitant extrapulmonary focus impossible. Of a group of seventy-four patients treated with the lamp, 31 per cent were cured (no roentgenologic signs of the disease could be detected any more) and 65 per cent were considerably benefited. These figures alone show that every one who treats tuberculous patients should study seriously the authors' methods of diagnosis and treatment.

CHEMISTRY AND RECENT PROGRESS IN MEDICINE. By JULIUS STIEGLITZ, Professor of Chemistry in the University of Chicago. Price, Cloth $1.50, Paper $0.75. Pp. 70. Baltimore: The Williams and Wilkins Company, 1926.

This little book contains the three Dohme Memorial Lectures which Professor Stieglitz delivered at Johns Hopkins University in May, 1923. It is, essentially, a sequel to the report of the Chemical Foundation in 1921 entitled "The Future Independence and Progress of American Medicine in the Age of Chemistry." It makes no pretense of being an exhaustive or critical survey of the many recent advances of chemistry in its application to medicine; it is, rather, a splendid and inspiring propagandum.

The author emphasizes what is not generally appreciated, namely, that the usefulness of the more fundamental sciences of chemistry and physics in the solution of medical problems is not restricted to their contribution to therapy

of such materials as ether and arsphenamine, nor to their assistance in the isolation of such important substances as insulin and the antitoxins. Perhaps the greatest advances may be expected from the carefully considered application of physicochemical laws to the elucidation of the mechanism of biologic processes. The clear, concise style is always most appealing. It becomes poignant in the discussion of the tragedy of senescence — the tragedy that man's capacity must become progressively impaired at the time of his greatest usefulness. The early isolation of those hormones that contribute to the working capacity, the ambition and the courage of youth is urged. Stress is laid, again and again, on the factor of timeliness in scientific discovery. The unfortunate hiatus of five centuries between the discovery of ether and its application in anesthesia is contrasted with the rapidity with which insulin has become incorporated into practical therapy since its discovery only a few years ago. The book is optimistic and inspiring.